

REMARKS

Second Preliminary Amendment

Claims 1-31 are pending. Upon entry of this amendment claims 32-34 will be added and claims 1-34 will be pending.

Support for the amendment of the claims to recite thalidomide, carmustine, prednisone, pamidronate, erythropoietin and bisphosphonate as a second therapeutic agent may be found in paragraph 93 of the specification where the diverse agents used in oncology practice are incorporated by reference from DeVita et al. (see also paragraph 181). As shown on the enclosed pages from DeVita et al., each of these agents is disclosed as being a therapeutic agent for use in the treatment of cancer (thalidomide at page 3083, carmustine at page 2359, pamidronate at page 2830, prednisone at page 2359, erythropoietin at page 2644, bisphosphonate at page 2579).

Support for the amendment of the claims to recite interferon alpha-2a as a second therapeutic agent may be found in paragraph 92 of the specification.

Support for the amendment of the claims to recite vincristine as a second therapeutic agent may be found in paragraph 83 of the specification.

Support for recitation of bortezomib (Velcade), doxorubicin, cyclophosphamide, interferon alpha-2b, zoledronate and dexamethasone in the new claims is support by the recitation of these agents in the pending claims (see, e.g., claim 2).

No new matter has been added. Entry of the Amendment is respectfully requested.

Response to Restriction and Election of Species Requirement

In response to the Restriction Requirement in the Restriction and Election of Species Requirement, dated August 7, 2006, Applicants elect **Group I** (claims 1-18 and 23) for examination on the merits. As new claims 32 and 33 depend from elected claims, claims 32 and 33 should be included in the elected group. This election is being made without traverse.

In response to the Election of Species Requirement as between the agents set forth in A-ZZ, Applicants elect **agent SS - Bortezomib (Velcade)**. As the examiner expands his search to additional agents, Applicants respectfully request that the examiner first search the following compounds that are related to Velcade in their ability to also treat multiple myeloma: melphalan, thalidomide, doxorubicin, cyclophosphamide, interferon alpha-2b, interferon alpha-2a, vincristine, carmustine, prednisone, zoledronate, pamidronate, erythropoietin, bisphosphonate and dexamethasone.

Elected claims 1, 2, 4-17, 23, 32 and 33 read on the elected species.

Upon allowance of product claims 1-18 and 23, Applicants respectfully request rejoinder of method claims 19-22, 24-31 and 34.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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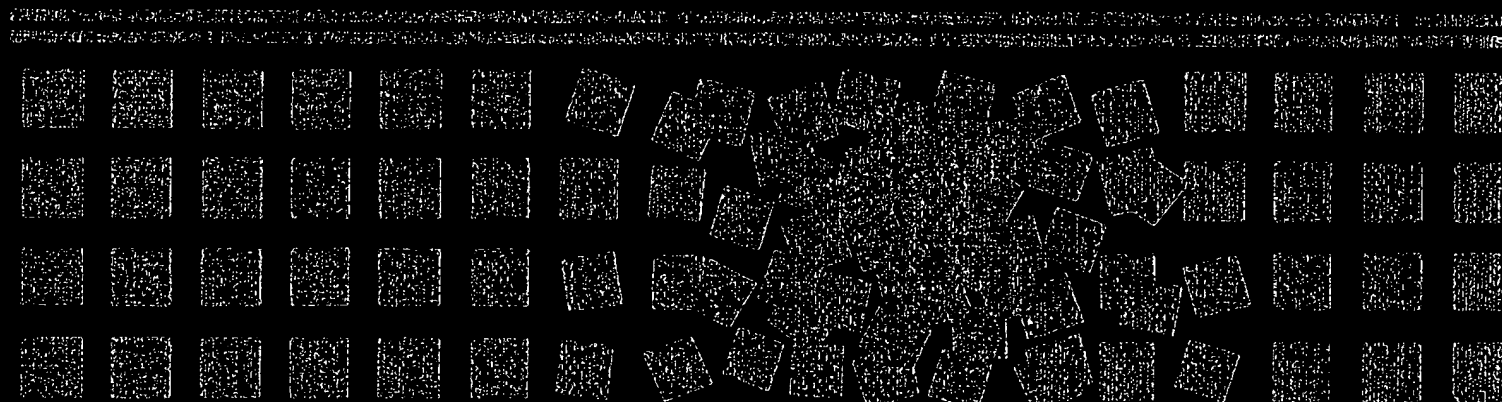
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Principles & Practice of Oncology



Volume 2

5th Edition

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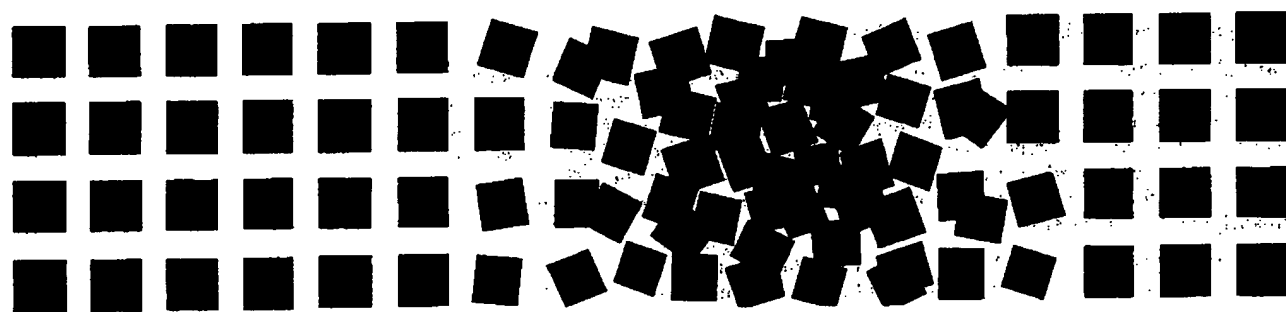
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The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care provider to ascertain the FDA status of each drug or device planned for use in their clinical practice.

mined from serum M-component levels) may progressively shorten; this may be analogous to the blast crisis phase of chronic myeloid leukemia.¹⁸⁴ Integration of tritiated thymidine-labeling index and tumor-burden studies defined these patients as having high-growth-fraction, high-tumor-burden myeloma.¹⁴⁰ This patient group has a poor prognosis, with rapid myeloma growth and early death.^{140,185} Patients whose myelomas have more rapid growth kinetics have a propensity for extramedullary tumor growth, including soft-tissue plasmacytomas and central nervous system (CNS) involvement. In some instances, the neoplasm takes on a less differentiated morphologic appearance, similar to that of a large cell lymphoma, with a cell surface Ig that usually corresponds with the prior serum Ig.^{97,186,187}

In earlier phases of disease, the quantity of M-component synthesis as determined from serum or urine measurements corresponds with the amount of tumor in the body. However, in the terminal phase, the M-component synthesis rate per tumor may decline or qualitatively change as the tumor progresses, suggesting the development of a mutant clone. Some patients who previously had only a serum M-component switch to primarily urinary light chains, reflecting additional biochemical abnormalities in Ig synthesis and assembly.¹⁸⁸

Unlike the aggressive forms of the disease, another subset of patients have indolent or smoldering myeloma in which, despite evidence of bone lesions, the disease progresses slowly even without treatment. These patients previously could be identified only from their clinical course; however, the use of tritiated thymidine-labeling studies usually identifies these patients as having hypoproliferative myeloma cells, with fewer than 0.5% of the tumor cells labeling and in a range similar to that of MGUS.^{139,140}

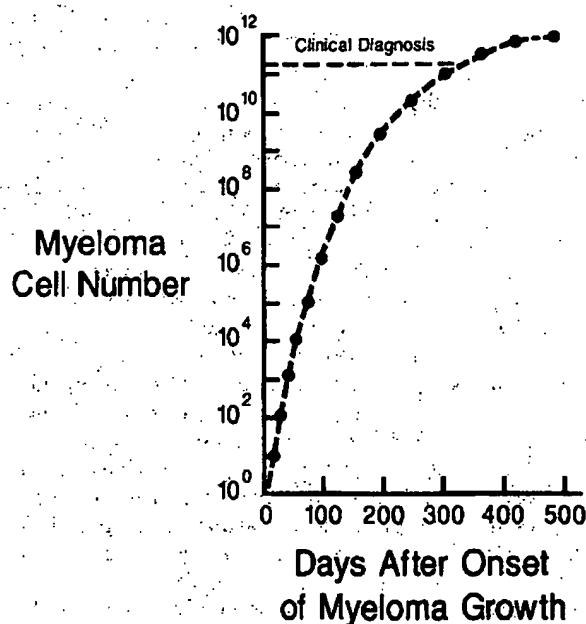


FIGURE 45.4-4. Gompertzian growth curve in multiple myeloma. In this untreated patient with IgG myeloma, serial measurements of M-component production were used to extrapolate the preclinical phase of myeloma cell proliferation of about 1 year.

DIAGNOSIS AND CLINICAL STAGING OF MYELOMA

Presenting symptoms and signs of myeloma usually include bone pain, which may be associated with compression fractures of the spine or pathologic fractures of long bones; weakness and anemia; and infection, usually due to pneumococcal or other gram-positive bacteria. Hypercalcemia, renal failure, spinal cord compression, or a mixture of these findings may be present. Punched-out osteolytic bone lesions are commonly seen on skeletal x-ray films (see Fig. 45.4-3). A complete skeletal x-ray series, including the axial and appendicular skeleton, should always be obtained at the time of diagnosis. Only in this way can the number and location of lesions be identified to determine if any potentially unstable osteolytic lesions are present.

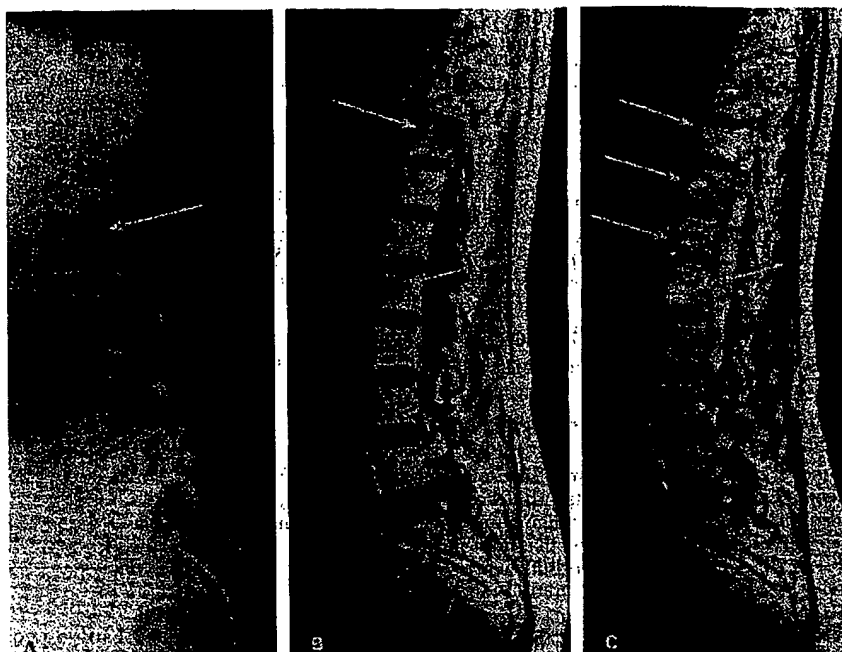
Studies using magnetic resonance imaging (MRI) scanning suggest that this approach can provide greater detail on myelomatous abnormalities in the vertebral column than conventional radiographs (Fig. 45.4-5). Some characteristic MRI patterns of change in myelomatous marrow involvement have also been identified at diagnosis and after chemotherapy.^{189,190} However, because this procedure is expensive and takes several hours to acquire the imaging information on the entire spine of a single patient, this technique must be used selectively.¹⁹¹ Bone scans are of no value in the assessment of skeletal involvement in myeloma because the bone disease is almost purely osteolytic and the nuclear medicine isotopes are taken up only in areas of osteoblastic activity.

An increase in the number of plasma cells is usually demonstrable in the bone marrow or in a biopsy of a plasmacytoma. A serum or urinary M-component can be demonstrated in 99% of the patients. However, in some instances, not all criteria are present, and a mixture of criteria is needed to establish a diagnosis of multiple myeloma and to differentiate it from other plasma cell disorders. Useful diagnostic criteria are summarized in Table 45.4-3.

A clinical staging system for multiple myeloma was developed at the Arizona Cancer Center by Durie and Salmon by analyzing the presenting features of a series of patients with multiple myeloma who had their tumor burden directly measured using the metabolic techniques.¹⁹² On the basis of these clinical correlations, multiple myeloma was divided into three tumor burden groups: stage I (low), II (intermediate), and III (high). Tumor mass stage alone was predictive of survival. An additional prognostic factor, renal function, independently influenced survival and was included in the staging system, with normal renal function (i.e., serum creatinine less than 2.0 mg/dL or blood urea nitrogen less than 30) as substage A and higher values as substage B (Table 45.4-4).

Several other investigations applied the Durie-Salmon myeloma staging system to evaluate survival by stage in myeloma (Table 45.4-5). In studies of response to treatment and survival, the clinical features that correlated with a given stage in terms of tumor burden predicted survival in the original patients and in subsequent reports by other investigators in large groups.^{197,203,204} Figure 45.4-6 depicts the influence of clinical stage and renal function on the survival of patients with multiple myeloma. In the original study used in developing the Durie-Salmon myeloma staging system, the percentage of bone marrow plasma cells was an important factor, but it was not

FIGURE 45.4-5. Radiograph of lower spine (A) compared with magnetic resonance images (B and C). The osteolytic lesions in the vertebral bodies of T10-12 and L1 that were poorly visualized on plain films were much more visible on the T1-weighted (B) and T2-weighted (C) MR images. (Ludwig M, Tscholakoff D, Neuhold A, et al. Magnetic resonance imaging of the spine in multiple melanoma. *Lancet* 1987;2:36)



included in the staging system because it could be replaced by other clinical features and was potentially susceptible to sampling errors. Bone marrow involvement was deleted from the staging criteria after consideration of the potential difficulties that might be encountered in accurately and reproducibly counting plasma cells in the bone marrow differential at different centers. Patients with Bence Jones-only myeloma have been assessed for measured tumor cell burden, and they appear to represent a higher risk subgroup with a higher tumor cell mass and shorter survival.²⁰⁵ One of the more challenging patient populations on which to prognosticate is the group with asymptomatic stage I myeloma. Although this group has a good prognosis, recent efforts have been made to identify prognostic factors that will predict which patients will have progressive disease requiring treatment.²⁰⁶ In this analysis, the only significant factors to identify patients who would progress were hemoglobin levels less than 12 g/dL, bone marrow plasmacytosis greater than 25%, and M-component levels of 3.0 g/dL or more for IgG or of 2.5 g/dL or more for IgA. Patients without one of these adverse factors remained free of disease progression for more than 50 months.

DIFFERENTIAL DIAGNOSIS

The criteria shown in Table 45.4-3 provide the basis for differentiating myeloma from other major plasma cell disorders with M-component secretions other than IgM. The IgM M-components are usually attributable to Waldenström's macroglobulinemia and occasionally to MGUS or other entities. Multiple myeloma with IgM secretion has rarely been reported, and it should be diagnosed only if the patient has multiple osteolytic bone lesions that contain monoclonal plasma cells.⁹⁷ Marrow plasmacytosis is observed in several chronic infectious or inflammatory diseases and in hypersensitivity reactions, autoimmune disease, unrelated neoplasms, and occasionally in other

conditions; it is not associated with secretion of an M-component, but it is associated with polyclonal hyperglobulinemia.

The major differential diagnosis is usually between myeloma and MGUS. There is an overlap between the findings for patients with MGUS and those with stage I myeloma (or macroglobulinemia) that can often be recognized only by serial follow-up of the patient for at least 1 year without any form of treatment. In MGUS, the M-component level remains constant over many years, but in the malignant plasma cell disorders, the M-component gradually rises, and other symptoms and signs of the disease develop. A policy of watch and wait is completely justifiable, because there is no evidence that treatment improves the outcome in stage I myeloma or MGUS, and the use of chemotherapy has potential hazards that should be avoided if the patient does not have an invasive, progressive plasma cell malignancy. The schema developed by Facon and colleagues²⁰⁶ for identifying which patients with stage I myeloma might benefit from earlier treatment is worthy of consideration. If, after a year's follow-up of the patient's M-component and symptoms and signs at 1- to 2-month intervals, there is no evidence of progression, the most likely diagnosis is MGUS, and follow-up examinations should be done at least annually because approximately 2% of these patients progress to a diagnosis of B-cell neoplasm each year.¹

Patients presenting with only Bence Jones proteinuria usually have myeloma alone or with amyloidosis.^{207,208} It has been stated that its excretion has "sinister significance."²⁰⁹ However, Bence Jones MGUS has been reported and followed without specific therapy for several years in a few patients.^{170,210} It is nonetheless reasonable to have a higher index of suspicion when patients present with idiopathic Bence Jones proteinuria, because it usually progresses within 6 months to 1 year to clearly diagnosed myeloma, which should be treated appropriately. Patients with unrelated metastatic neoplasms occasionally have MGUS, and a series of diagnostic studies and biopsies

TABLE 45.4-3. Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Unknown Significance^{139,170,194,195}**MULTIPLE MYELOMA****Major Criteria**

Plasmacytoma on tissue biopsy

Bone marrow plasmacytosis with >30% plasma cells

Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for G peaks or 2 g/dL for A peaks, ≥ 1 g/24 h of κ - or λ -light chain excretion on urine electrophoresis in the presence of amyloidosis**Minor Criteria**

Bone marrow plasmacytosis 10% to 30% plasma cells

Monoclonal globulin spike present but less than the level defined above

Lytic bone lesions

Residual normal IgM <50 mg/dL, IgA < 100 mg/dL, or IgG <600 mg/dL

Diagnosis is confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b, i.e.:

I + b, I + c, I + d (I + a not sufficient)

II + b, II + c, II + d

III + a, III + c, III + d

a + b + c, a + b + d

INDOLENT MYELOMA (SAME AS MYELOMA EXCEPT)No bone lesions or only limited bone lesions (≤ 3 lytic lesions): no compression fractures

M-component levels: (a) IgG <7 g/dL; (b) IgA <5/dL

No symptoms or associated disease features, i.e.:

Performance status >70%

Hemoglobin >10 g/dL

Serum calcium normal

Serum creatinine <2 mg/dL

No infections

SMOLDERING MYELOMA (SAME AS INDOLENT MYELOMA EXCEPT)

No bone lesions

Bone marrow plasma cells $\leq 30\%$ **MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE**

Monoclonal gammopathy

M-component level

IgG ≤ 3.5 g/dLIgA ≤ 2 g/dLBJ protein ≤ 1 g/24 h

Bone marrow plasma cells <10%

No bone lesions

No symptoms

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; BJ, Bence Jones light chain.

is required to establish that the patient does not have myeloma. Myeloma and an unrelated metastatic neoplasm may be diagnosed.

 β_2 -MICROGLOBULIN

β_2 -Microglobulin is an important prognostic factor in multiple myeloma.²¹¹ It is a low-molecular-mass protein, which is the

light chain of the HLA antigen and is synthesized by all nucleated cells.²¹² It falls in the class of tubular proteins that pass the glomerulus and are excreted in the urine, but renal functional impairment elevates the serum level of β_2 -microglobulin. β_2 -Microglobulin can be measured by radioimmunoassay. If corrected for renal function, serum β_2 -microglobulin levels correlate strongly with tumor burden in multiple myeloma.^{211,213-217} Because the serum levels are a function of myeloma cell mass and renal function, measurement of β_2 -microglobulin may provide an alternative to clinical staging for predicting survival.²¹⁸ The relation of β_2 -microglobulin to survival in myeloma is depicted in Figure 45.4-7. β_2 -Microglobulin can serve as a pretreatment prognostic factor in clinical trials because it permits a more direct comparison of risk factors among the various cooperative groups and institutions interested in myeloma therapy.^{219,200} Although it has been proposed that β_2 -

TABLE 45.4-4. Myeloma Staging System

Criteria	Measured Myeloma Cell Mass (Cells $\times 10^{12}/m^2$)
STAGE I	
All of the following:	<0.6 (low)
Hemoglobin value >10 g/dL	
Serum calcium value normal (<12 mg/dL)	
On roentgenogram, normal bone structure (scale 0) or solitary bone plasmacytoma only	
Low M-component production rates	
IgG value <5 g/dL*	
IgA value <3 g/dL	
Urine light chain M-component on electrophoresis <4 g/24 h	
STAGE II	
Overall data not as minimally abnormal as shown for stage I and no single value as abnormal as defined for stage II	0.6-1.2 (intermediate)
STAGE III	
One or more of the following	>1.2 (high)
Hemoglobin value < 8.5 g/dL	
Serum calcium value >12 mg/dL	
Advanced lytic bone lesions (scale 3)	
High M-component production rates	
IgG value >7 g/dL	
IgA value >5 g/dL	
Urine light chain M-component on electrophoresis >12 g/24 h	
Subclassification	
A = relatively normal renal function (serum creatinine value >2 mg/dL)	
B = abnormal renal function (serum creatinine value ≥ 2 g/dL)	
Examples	
Stage IA: low cell mass with normal renal function	
Stage IIB: high cell mass with normal renal function	

* IgA, immunoglobulin A; IgG, immunoglobulin G. (Alexanian R, Balcerzak S, Bonnet JD, et al. Prognostic factors in multiple myeloma. Cancer 1975;36:1192)

TABLE 45.4-5. Median Survival in Relation to Stage at Diagnosis

Investigation	Patients	Median Survival (mo) by Stage				
		I	II	III	A	B
Durie & Salmon ¹⁹²	71	>60	50	26		
Alexanian et al ¹⁹⁶	343	39	27	17		
Woodruff et al ¹⁹⁷	237	64	32	6	21	2
Merlini et al ¹⁹⁸	123	76	41	12		
Belpomme et al ¹⁹⁹	118	>60	28	7	>60	12
Gobbi et al ²⁰⁰	91	>79	51	33		
Santoro et al ²⁰¹	81	48	41	23	35	7
Bergsagel et al ²⁰²	364	46	32	23	32	11
Total	1428	>60	41	23		

microglobulin can be used to differentiate between MGUS and myeloma, significant overlap prevents this.^{211,214,221} Serial β_2 -microglobulin levels have not proven to be as useful as M-component measurements after response to treatment of myeloma. IFN- α is reported to raise β_2 -microglobulin levels in myeloma.²²² In our own experience, β_2 -microglobulin has not proved useful in patients lacking an M-component (nonsecretory myeloma).

TREATMENT

PRINCIPLES

The diagnosis of a monoclonal gammopathy does not represent an immediate mandate for treatment, and patients with MGUS, stage I myeloma, and indolent or smoldering myeloma are often best followed without treatment until it is warranted by the development of clear-cut progression of the disease.

Because multiple myeloma is a disseminated plasma cell neoplasm, the primary approach to treatment is systemic antineoplastic therapy. Symptoms and signs that warrant immediate institution of therapy include the development of bone pain, hypercalcemia, renal failure, severe suppression of bone mar-

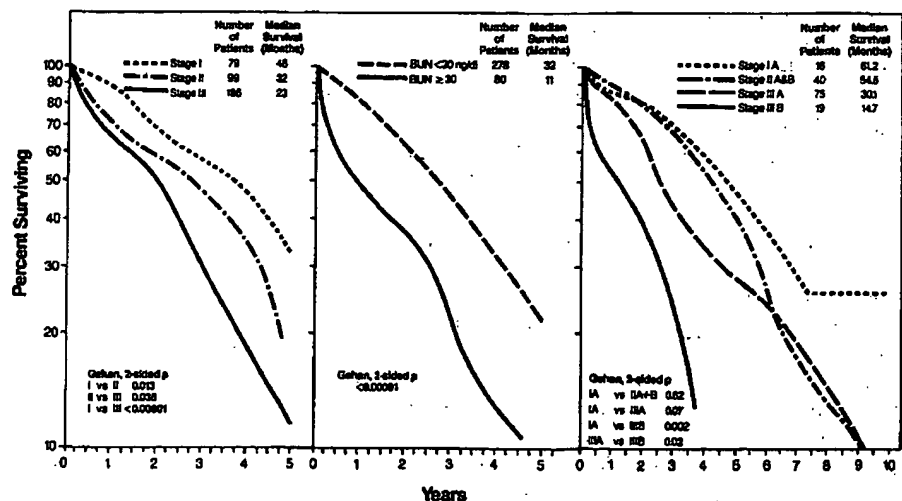
row functions, or spinal cord compression. If the patient has spinal cord compression, completion of local therapy (usually with radiation therapy) should normally precede the initiation of systemic chemotherapy unless other serious complications mandate simultaneous systemic treatment and radiation therapy. Patients presenting with long-bone fractures should have them internally fixed orthopedically before the initiation of chemotherapy. Presentation with constellations of findings, such as marked anemia plus the presence of lytic bone lesions, bacterial sepsis, or Bence Jones proteinuria, provide reasons for initiation of therapy. If there is significant infection, initiation of treatment should usually be delayed until the infection has been controlled. If the clinical findings are ambiguous, a period of observation that includes serial M-component measurements is usually warranted.

Doubling in the M-component in less than 1 year with other clinical findings of myeloma can also be used as a basis for treatment. For example, patients with rising M-component levels or progressive bone lesions are candidates for treatment even if they are asymptomatic. Useful adjuncts to systemic treatment include management of local problems with radiation therapy and a variety of supportive care measures.

Beneficial effects of systemic therapy can be obtained in most patients with newly diagnosed progressive myeloma in clinical stages II or III. The best improvement in survival of patients with myeloma has been obtained for those with stage III disease. The clinical phases of myeloma under treatment include an initial drug sensitive phase, which is observed in most patients; a plateau phase, during which tumor burden is reduced and appears to be stable during maintained or unmaintained remission; and an eventual drug-resistant phase, during which the neoplasm may exhibit altered growth kinetics and resistance to conventional cytotoxic drugs.^{2,225} About 15% to 20% of patients manifest resistance even to aggressive parenteral chemotherapy at the time of initial presentation with progressive myeloma.

Systemic therapy usually relieves bone pain relatively promptly, but many other aspects of the disease improve gradually and may require other supportive measures initially. Even with prompt institution of systemic treatment, the drug-sensitive phase of disease usually lasts only 2 to 3 years for most

FIGURE 45.4-6. Influence of clinical stage and renal function on survival of patients with plasma cell myeloma as redrawn from published illustrations. The left two panels are from a Canadian NCI study²⁰³ and show the separate effects of clinical stage and renal function, respectively. The right panel depicts an Arizona Cancer Center study, and the survival curves are shown with clinical stage and renal function integrated with the use of the clinical staging system shown in Table 45.4-4. Statistical comparisons of survival outcome for the various stages and risk groups in the studies appear in each panel. BUN, blood, urea, nitrogen.



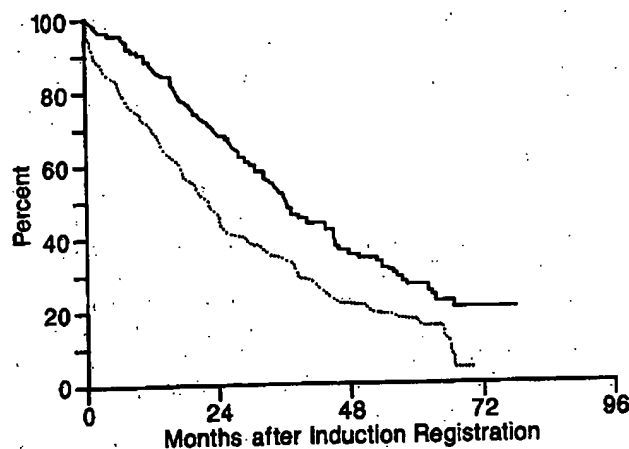


FIGURE 45.4-7. Life table survival curves in multiple myeloma in relation to serum β_2 -microglobulin (β_2 M) concentration. The upper curve (solid line) is for 324 patients with a serum concentration of less than 6 g/mL (median survival, 36 months). The lower curve (dotted line) is for 224 patients with higher serum levels (median survival, 22 months; $P < .0001$). (Salmon SE, Tesh D, Crowley J, et al. Chemotherapy is superior to sequential hemibody irradiation for remission consolidation in multiple myeloma: a Southwest Oncology Group study. *J Clin Oncol* 1990;8:1575)

patients before drug resistance manifests. Although the median survival before the era of effective systemic therapy was less than 1 year, it is now in the range of 3 to 4 years. In a few patients, sensitivity to systemic therapy may persist for 5 to 10 years or longer.

Care must include maximal efforts to relieve pain, hypercalcemia, severe anemia, and various local complications promptly to keep the patient from being bedridden, minimizing bone demineralization and superinfections. Patients should be encouraged to drink several liters of fluid daily to avoid dehydration and enhance urinary excretion of light chains and calcium.

EVALUATION OF RESPONSE TO TREATMENT

Because myeloma has a variety of clinical manifestations, a series of initial and follow-up studies is needed to assess the response to systemic treatment. These include a thorough history, physical examination, and following laboratory studies, which include the complete blood count with differential and platelet counts; M-component levels in the serum, 24-hour urine, or both; serum calcium, creatinine, or blood urea nitrogen levels; and skeletal radiographs. Although serum electrophoresis is extremely useful in the initial diagnostic workup, baseline and follow-up quantitation of the serum M-components is most reliably measured using laser nephelometry of the involved immunoglobulin. Serum electrophoresis is sometimes a useful alternative, particularly as the M-component level approaches the normal range for the involved Ig. The radial immunodiffusion test should not be used to measure myeloma immunoglobulins, because it has not proved reliable. Quantitation of urinary Bence Jones protein is best determined by protein electrophoresis using a 24-hour concentrate. The relative value of β_2 -microglobulin useful for following the course of myeloma has not been established, but β_2 -microglob-

ulin is not as specific as M-component measurements, because its serum concentration is affected by tumor burden and renal function.

In the absence of specific symptoms, follow-up radiographs should be obtained every 6 to 12 months. The initial skeletal x-ray evaluation before therapy should include a complete metastatic survey, because myelomatous involvement can be located in any area of the axial or appendicular skeleton. Isotopic bone scans are of little or no value for myeloma and are not recommended. Bone marrow involvement should be assessed initially with an aspirate and a core bone marrow biopsy. Caution is needed to avoid excessive pressure on the needle when the needle is inserted, because in some myeloma patients, the bone matrix is extremely fragile. Follow-up bone marrow specimens are obtained to confirm remission status after therapy and to explain an unexpected pancytopenia. Marrow involvement with myeloma is usually diffuse, but occasionally it is spotty and may be subject to sampling error for needle aspiration but usually not for core biopsy. "Dry taps" on aspirates can be due to needle placement within a plasmacytoma. Table 45.4-6 summarizes a useful schedule for obtaining initial and follow-up studies in myeloma patients.

M-component production usually correlates with tumor burden in myeloma patients, and its serial assessment usually provides an excellent guide to the response to treatment or disease progression. Objective response criteria should identify patients who have achieved significant tumor regression and separate them from patients who have only stabilized or who have had symptomatic improvement without having achieved remission status. In 1973, the Leukemia-Myeloma Task Force of the NCI published the criteria for response in myeloma, which required a 50% reduction in the serum or urinary levels of an M-component to define remission.²²⁴ Although the task force criteria were created to identify groups of patients responsive to treatment, they were developed before the acquisition of detailed knowledge of Ig metabolism. Analysis of Ig metabolism led to the recognition that for the major classes of IgG (IgG1, IgG2, and IgG4, which comprise 90% of serum IgG), metabolism is not linear with the serum concentration.²²⁵ With a relatively high serum IgG M-component value, the half-life of IgG may be as short as 8 to 10 days, but with a low value, the half-life may be 40 days or longer. This concentration-dependent phenomenon applies to IgG M-component levels in 90% of patients with IgG myeloma or approximately 50% of all myeloma cases. Comparisons of serum levels in these patients underestimate the degree of change, depending on the initial and follow-up serum M-protein values.² Correction can be made for changes in the metabolic rate for IgG through the calculation of a synthetic index from the serum values.²²⁶ A useful nomogram for this purpose has been derived from the metabolic equations.² A nomogram with an extended scale for IgG values appears in Figure 45.4-8.

Assessment of urinary light chain excretion is affected significantly by the degree of catabolism that takes place in the kidney, which is a function of the absolute levels of light chains passing the glomerulus and the degree of renal functional impairment.²⁰⁵ To avoid difficulties in assessment, criteria for improvement in Bence Jones proteinuria must be quite stringent. The response criteria adopted by SWOG are summarized in Table 45.4-7. Response in accord with the SWOG criteria is strongly correlated with improvement in survival. Patients

whose hemoglobin, renal function, and albumin levels improve have a better outcome than if the clinical variables remain unchanged or worsen. Responsive patients have improvement in general well-being and in ambulation, and they have marked relief of symptoms of bone pain. However, recalcification of osteolytic bone lesions is observed in fewer than 5% of patients who respond to conventional chemotherapy.

A retrospective analysis of 69 stage II and 80 stage III myeloma patients treated at a single institution was evaluated with Myeloma Task Force and SWOG response criteria.²²⁷ In carrying out this analysis, 2 stage II patients and 9 stage III patients who failed to live 3 months were censored to minimize the "guarantee time" inherent in including early deaths as nonre-

TABLE 45.4-6. Checklist of Laboratory Studies for Patients With Multiple Myeloma

ROUTINE PRETREATMENT EVALUATION

Complete blood count, differential, and platelets
Serum protein electrophoresis
Serum immunoglobulins (nephelometry)
Serum β_2 -microglobulin
24-h urine for total protein and electrophoresis
Antigenic typing of serum and urine monoclonal immunoglobulins by immunofixation or immunoelectrophoresis
Bone marrow aspiration and biopsy
Serum creatinine
Serum calcium
Serum electrolytes
Serum uric acid
Liver functions
Chest radiograph
Skeletal x-ray survey (entire skeleton)
Electrocardiogram

SPECIALIZED STUDIES FOR SELECTED PATIENTS

Abdominal fat pad or rectal biopsy for amyloid (also tap joint effusions for amyloid)
Solitary lytic lesion, soft tissue or lymph node biopsy
Serum viscosity if IgM component present or if any serum M-component > 7 g/dL
Plasma volume if serum relative viscosity > 4
Myelogram (or in some instances MRI) if paraspinal mass or symptoms and signs of spinal cord or nerve root compression (spinal fluid should be sent for cell count, cytosin differential, glucose, and protein)

ROUTINE FOLLOW-UP STUDIES

Before every course of treatment:
CBC, differential, platelets (should be repeated to check nadirs on first few courses)
At least every 3 mo (and on completion of induction or change to alternative therapy for refractory patients):
Serum monoclonal immunoglobulins by nephelometry or electrophoresis
24-h urine protein electrophoresis (if Bence Jones protein present)
Serum chemistry panel
At least annually:
Skeletal x-ray survey (entire skeleton), chest film, serum β_2 -microglobulin
Bone marrow aspiration if any significant abnormality in blood counts, immunoglobulins, or new symptoms
Serum immunoglobulins (nephelometry)

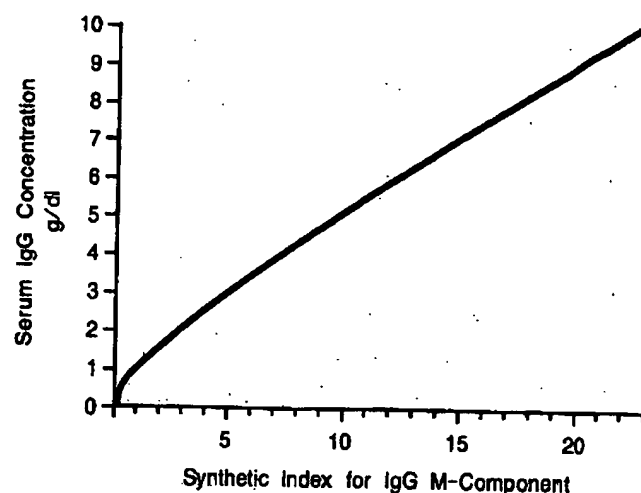


FIGURE 45.4-8. Nomogram for determining the synthetic index for IgG M-components of subclasses IgG1, IgG2, and IgG4, which comprise 90% of IgG myelomas. Using the patient's initial serum IgG concentration on the vertical axis, read down from the line to the horizontal axis to determine the synthetic index for that IgG value (Syn1). The same procedure is followed for the follow-up value (Syn2). $\text{Syn2/Syn1} \times 100 = \% \text{ of baseline synthetic index and tumor burden}$. This nomogram corrects for concentration-dependent changes in M-component synthesis and myeloma cell mass and gives a more accurate assessment of changes in tumor burden in IgG myeloma than can be calculated directly from the serum levels. The nomogram is not required for IgG3, IgA, IgD, or IgM serum M components, and changes in serum values for these Igs can be used directly to determine the percent change in tumor burden. The equation used to develop this nomogram has been incorporated into a program for a pocket calculator to calculate tumor cell mass. (Salmon SE, Wampler SE. Multiple myeloma: Quantitative staging and assessment of response with a programmable pocket calculator. *Blood* 1977;49:379)

sponders by usual statistical methods. The researchers concluded from this analysis of a relatively small series of patients that the Myeloma Task Force criteria of response may have similar predictive value to that of the SWOG for stage II patients. They found that the SWOG criteria had greater predictive value for stage III patients but believed that the latter difference was of questionable significance. Further analysis of significantly larger patient populations is warranted to authenticate the association of M-component reduction and tumor regression in multiple myeloma. Criteria for "true complete remissions" have more recently been applied to studies of high-dose therapy associated with stem cell autografting or allografting. For example, the criteria defined by Gore and colleagues²²⁸ require that no M-component be measurable by serum or urine electrophoresis and the bone marrow aspirate have fewer than 5% plasma cells. Other groups have more stringent criteria, requiring absence of the M-component on immunoelectrophoresis or immunofixation.²²⁹

RADIATION THERAPY

Palliation for Bone Pain and Soft Tissue Masses

Radiation therapy has been recognized for many years as a rapid and highly effective palliative agent in the treatment of multiple myeloma.²³⁰⁻²³⁴ Despite advances in the systemic treatment of this disease, radiation therapy continues to be

TABLE 45.4-7. SWOG Myeloma Response Criteria

Responsive patients who satisfy all of the following criteria are considered to have achieved definite objective improvement:

- A sustained decrease in the synthesis index of serum M protein to 25%, or less, of the pretreatment value on at least two measurements separated by 4 wk. For IgA and IgG3 M-proteins, the synthetic index is the same as the serum concentration. For IgG M-proteins of subclasses 1, 2, and 4, the synthetic index must be estimated using the nomogram shown in Figure 47-6.
- A sustained decrease in 24-h urine globulin to 10%, or less, of the pretreatment value, and to less than 0.2 g/24 h on at least two occasions separated by 4 wk.
- In all responsive patients the size and number of lytic skull lesions must not increase, and the serum calcium must remain normal. Correction of anemia (hematocrit >27 mg/dL) and hypoalbuminemia (>3 g/dL) is required if they are considered to be secondary to myeloma.
- With equivocal data (e.g., nonsecretors, L chain producers for whom the pretreatment urine collection was lost), the following support the conclusion that an objective response has occurred:
 - Recalcification of lytic skull lesions
 - Significant increments in depressed normal immunoglobulins (e.g., increments >200 mg/dL IgM, >400 mg/dL IgA, and >4000 mg/dL IgG)

Improved patients show a decline in the serum M-protein synthesis rate to less than 50%, but not less than 25% of the pretreatment value. Unresponsive patients fail to satisfy the criteria for responsive or improved patients.

(After Alexanian R, Bonnet J, Gehan E, et al. Combination chemotherapy for multiple myeloma. *Cancer* 1972;30:382)

important. It has been estimated that almost 70% of all patients eventually require and potentially benefit from treatment with irradiation.²³⁵

Treatment of painful, disabling bony sites is usually rapidly successful because of the radioresponsive nature of myeloma. In addition to rapid relief of pain, with accompanying decrease in narcotic requirements, pain relief allows patients to maintain much more normal activity, reducing the structural weakness in bone caused by calcium loss from bedrest. Because treatment is often rapidly effective at relatively modest doses, irradiation can arrest local tumor progression in bone and prevent pathologic fractures, minimizing the morbidity of more invasive therapeutic interventions for these patients. These positive features of irradiation enable a much more normal functional existence for patients.²³⁰⁻²³³

Myeloma is usually quite responsive to radiation therapy, and tumor doses of approximately 2000 to 2400 cGy in five to seven fractions over 1 to 1.5 weeks are usually sufficient.²³¹⁻²³³ Relief of pain is obtained in more than 90% of treated patients.^{235,236} From 30% to 65% of responses are complete.²³⁵ An analysis of 100 patients treated at the University of Arizona demonstrated no increase in response probability with doses greater than 1500 cGy. Limited numbers of sites were treated with lower doses. Neither the probability of recurrent symptoms nor the time to relapse at the treated site was influenced by the radiation dose. Except for solitary disease, higher doses have not been advantageous, and because of the generalized nature of the disease and its relatively long natural history, higher doses may preclude a necessary second course of treat-

ment to a site caused by tumor reseeded, extension, or regrowth.

Careful treatment planning is necessary to ensure inclusion of the entire lesion(s) responsible to the localized problem, and imaging studies such as computed tomography (CT) scans may be helpful in delineating the extent of tumor.

Judgment and experience are necessary in determining when radiation therapy is appropriate (versus systemic treatment); especially early in the course of this often chronic condition. Although irradiation relieves the most disabling symptom(s), a similar result often can be achieved by chemotherapy, especially early in the course of myeloma, with no resultant compromise in future delivery of chemotherapy because of myelosuppression. This is particularly true in the treatment of sites containing considerable bone marrow, such as the pelvis. A Cancer and Leukemia Group B (CALGB) study that attempted "total bone marrow" treatment by sequential irradiation in combination with chemotherapy was not beneficial.²³⁷ Recirculation of myeloma into previously treated sites may partially explain the negative study.²³⁸ Ideal management requires close coordination with the physician administering the patient's systemic chemotherapy.

Structural changes brought about by tumor involvement may, by nerve compression or orthopedic instability, be responsible for a substantial portion of a patient's pain. It is usually a mistake to treat a patient with multiple myeloma to progressively higher doses than those previously used if some level of pain persists, assuming that careful prior imaging studies and treatment planning have been accomplished.

Special Indications for Radiation Therapy

Several other localized manifestations of myeloma may be indications for palliative irradiation, especially in the patient who has proved resistant to most conventional systemic agents. Included are patients who present with proptosis caused by sphenoid or orbital bone involvement, those who present with dental or facial abnormalities caused by maxillary or mandibular involvement, or those who present with CNS symptoms caused by extensive calvarial or base of the skull involvement. A treatment philosophy and approach similar to that for palliation of bone pain is appropriate.

CHEMOTHERAPY

Induction Therapy

The initial approach to treatment for most patients with symptoms and signs of progressive disease is with systemic chemotherapy. Cycle-nonspecific cytotoxic drugs, particularly alkylating agents, represent the current mainstay of standard therapy. Bifunctional alkylating agents, particularly melphalan and cyclophosphamide; nitrosoureas, including carmustine and lomustine; doxorubicin; and glucocorticoids represent the major active agents used in systemic therapy for multiple myeloma.^{23,26,27,239,240} Vincristine has been used in several treatment programs and although there is evidence it can reduce tumor burden somewhat, there is no indication that its addition to other drugs increases survival.²⁴¹⁻²⁴³ IFN- α has very limited single-agent antitumor activity in myeloma.²⁴⁴⁻²⁴⁹ All of these agents have been subjected to clinical trials as single agents in

myeloma and have also been incorporated into various combinations for evaluation in previously untreated patients.

Remission-Induction Chemotherapy

ALKYLATING AGENTS WITH OR WITHOUT GLUCOCORTICOIDS. A variety of simple alkylating agent-steroid combinations, as well as more complex regimens, have been used for remission induction for patients with multiple myeloma. Overall objective response rates in various series using single alkylating agents alone or in combination with prednisone usually are 50% to 70%, and the rates are influenced by the response criteria used and the aggressiveness with which the regimens can be administered because of their myelosuppressive effects. **Prednisone** and other glucocorticoids (e.g., methylprednisolone, dexamethasone) have been combined with alkylating agents because of their single-agent activity, lack of overlapping toxicity, and the suggestion that they may potentiate the action of other agents. In most instances, patients in these trials received maintenance chemotherapy after remission induction.

Many studies used a variety of schedules of oral administration of melphalan or cyclophosphamide alone or in combination with prednisone, with generally similar therapeutic results. Useful dosage schedules for the commonly used alkylating agents at conventional dosage levels appear in Table 45.4-8. Dosage adjustments for myelosuppression are commonly employed, but dose escalation in the absence of myelosuppression is not usually followed satisfactorily. Inadequate dose escalation (particularly with melphalan) can produce significant underdosing. Melphalan has variable absorption by the oral route, and the drug is best absorbed when ingested on an empty stomach.²⁵⁰ Although oral absorption is not usually a problem with oral cyclophosphamide or lomustine, regular monitoring of

the leukocyte count and differential count can detect patients with compliance problems with the self-administration of oral agents. Nadir absolute granulocyte counts below 2000/ μ L should be achieved between intermittent courses of therapy, but with continuous courses, the dosage should be adjusted to maintain the leukocyte count between 2000 and 3500/ μ L. Although intravenous schedules provide more predictable dose delivery, the largest experience has been with oral regimens. More recently, alkylating agents have been incorporated into substantially higher dosage chemotherapy regimens that require autologous hematopoietic stem cell support. Such regimens will be described later in this chapter.

Regardless of the dosage schedules or objective response rates in major clinical trials, the median survival time of patients receiving oral melphalan or cyclophosphamide alone or in combination with prednisone has ranged from 18 to 36 months, with an overall median of about 24 months (Table 45.4-9). Some "response rates" have varied because different criteria were used to determine objective response in the reported studies. Similar results have been observed with the nitrosoureas, although these agents have not been studied extensively.²⁶

The survival outcome in myeloma patients is now clearly superior to that observed before the introduction of alkylating agents, when median survival times from diagnosis were in the range of 3.5 to 11.5 months.²⁵¹⁻²⁵³ The improvement in survival that occurred in myeloma after the introduction of the alkylating agents is due to these drugs, rather than to changes in earlier diagnosis or changes in supportive care. Equivalent therapeutic effects have been reported with intermittent and continuous schedules. An initial loading dose followed by a subsequent continuous dose produces similar results.²⁵ Intermittent schedules may have advantages in terms of assuring regular monitoring of the patient's progress and avoiding cumulative toxicity.

TABLE 45.4-8. Conventional Intermittent Schedules of Alkylating Agents for Treatment of Myeloma Alone or in Combination With Prednisone

Route	Dose and Schedule
CYCLOPHOSPHAMIDE	
IV	1000 mg/m ² (27 mg/kg) q 3 wk
Oral	250 mg/m ² /d \times 4 d q 3 wk
MELPHALAN	
IV	16 mg/m ² q 2 wk \times 4 then q 4 wk Reduce initial dosing by 50% if serum creatinine > 2 mg/dL (BUN > 30 mg/dL)
Oral	8 mg/m ² q 3 wk or 9 mg/m ² q 4 wk (Because of varying bioavailability of oral melphalan, the dose must be increased to induce hematologic toxicity or significant underdosing may occur.)
CARMUSTINE (BCNU)	
IV	100-150 mg/m ² q 4-6 wk
LOMUSTINE (CCNU)	
Oral	130 mg/m ² q 4-6 wk

BUN, blood urea nitrogen.

MULTIAGENT COMBINATION CHEMOTHERAPY. A number of studies have compared the simple oral melphalan plus prednisone (MP) or cyclophosphamide plus prednisone (CP) combinations with more complex multiagent regimens. Although a subset of these studies reports significantly better survival results than have been observed with the simple combinations, differences are generally minimal at best. Such studies were initiated because of preclinical evidence suggesting that combinations of alkylating agents may be potentiating because there are different mechanisms of membrane uptake and other potential differences in their mode of action and cellular cytotoxicity.²⁴⁵

Some of the most widely used multiagent combinations include the M2 protocol developed at Memorial Sloan-Kettering Cancer Center²⁶² and the alternating combination chemotherapy regimens developed by SWOG.²⁰⁴ In the initial SWOG report of alternating combinations, vincristine, melphalan, carmustine, and prednisone (VMCP) was alternated with vincristine, carmustine, doxorubicin, and prednisone (VBAP) or vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP).²⁰⁴ In subsequent trials, the alternation has been limited to VMCP and VBAP, because VBAP can reinduce remission in myeloma patients who have previously responded and relapsed from therapy with melphalan or cyclophosphamide

TABLE 45.4-9. Effects of Some Major Trials of Single Alkylating Agents Alone or in Combination With Prednisone on Survival in Multiple Myeloma

Investigations	Treatment* (Alkylating Agent Scheduled)	Patients	Response Rate (%) ^a	Median Survival From Start of Therapy (mo)
Alexanian et al ¹²⁵⁴	Melphalan (i)	82	49-59	23
Alexanian et al ¹²⁵⁵	Melphalan (d)	35	17-19	18
	Melphalan, prednisone (i)	79	-65	24
Bergsagel et al ¹²¹	Melphalan (d)	165	14	25
Bergsagel et al ¹²⁰³	Melphalan, prednisone (i)	100	72	28
Costa et al ¹²⁵	Melphalan (d)	60	-25	26
	Melphalan, prednisone (d)	71	-48	35
	Melphalan, prednisone + testosterone (d)	58	-54	24
Hoogstraten et al ¹²⁵⁶	Melphalan (d)	64	45	23
Hoogstraten et al ¹²⁵⁷	Melphalan (i)	48	45	26
Korst et al ¹²²	Cyclophosphamide (d)	165	-48	24.5
McArthur et al ¹²⁵³	Melphalan (d)	39	41	28
MRC 1st study ¹²⁵⁸	Melphalan (d)	133	NR	18
	Cyclophosphamide (d)	141	NR	18
MRC 2nd study ¹²⁵⁹	Melphalan, prednisone (d)	128	NR	20
	Cyclophosphamide (d)	124	NR	20
MRC 3rd study ¹²⁶⁰	Melphalan (i)	179	NR	20
	Cyclophosphamide (i) (intravenous)	174	NR	26

d, daily; i, intermittent; NR, not reported.

^a Response rates shown with Myeloma Task Force Criteria or approximated from published data.

combinations.¹²⁶³ The dosage schedules for these Memorial Sloan-Kettering and SWOG combination programs are summarized in Table 45.4-10. The fifth Medical Research Council (MRC) trial of alternating combination chemotherapy used drug dosages that were essentially identical with that of SWOG, with the deletion of vincristine and prednisone (see Table 45.4-10).¹²⁶⁴ In a recent SWOG study, the VMCP/VBAP regimen was compared with this same program as well as with the addition of alternate-day prednisone (50 mg) between chemotherapy courses (VMCPP/VBAPP) and to the vincristine, doxorubicin, dexamethasone (VAD) regimen.^{1265,1266}

Slight changes in dosages of the M2 regimen have been used in various series.¹²²⁰ With the M2 regimen, improved survival has been reported in a nonrandomized study in which survival was calculated from the date of diagnosis rather than from the onset of therapy.¹²⁶² Subsequent randomized studies carried out by the Eastern Cooperative Group (ECOG) in the United States and by a multihospital group from Denmark compared the M2 regimen to melphalan and prednisone.^{1267,1268} Both studies failed to show an overall survival advantage with the M2 regimen, although an update on the ECOG study reported improved survival for stage III patients.¹²⁶³

Two successive studies carried out by SWOG compared the alternating combination regimens to a simpler regimen of MP or vincristine cyclophosphamide, plus prednisone (VCP). In both studies quite similar advantages in terms of improved response rate and improved median survival were observed with the alternating combination compared with the simpler regimen.^{1204,1269} The second of SWOG's evaluations of alternating combinations demonstrated remarkably similar survival plots for the VMCP plus VBAP compared with the simpler VCP regimen. Analysis of pretreatment prognostic factors showed

that the treatment groups were quite comparable. A significantly larger proportion of patients responded to the alternating combinations, suggesting that the additional responsive patients may have required combination therapy to reach remission status and could be anticipated to have had a poorer prognosis and below-average remission duration. Analysis of the data on high-risk stage III patients in some studies supports this interpretation and is consistent with the overall remission duration in the VMCP-VBAP group being diluted with the addition of poor-risk patients "recruited into" the responsive category with the aggressive combination who would not have achieved remission with the simple regimens.¹²⁶²

A similar interpretation may apply to studies from ECOG and the CALGB, who found improved response rates, survival time, or both in specific subsets of patients with multiagent combinations compared with the MP regimen.^{1267,1270} In these two studies, overall survival for all patients was not improved, suggesting that the increased toxicity of the aggressive regimens may have a detrimental effect on survival of subsets of patients. The MRC study made an observation similar to that by SWOG. In the MRC study, 627 patients were randomized to receive almost identical schedules of the cytotoxic agents used in the SWOG VMCP-VBAP studies, except that vincristine and prednisone were omitted. The MRC study compared alternating melphalan plus cyclophosphamide and carmustine plus doxorubicin to melphalan alone. In the MRC study, the survival advantage for the 314 patients receiving the alternating combinations was significantly superior ($P = .0003$) to that obtained with melphalan alone.¹²⁶⁴ Curves for the MRC study are similar to the SWOG results despite the omission of vincristine and prednisone. The MRC's comparison of ABCM to melphalan is significantly larger than the SWOG study or other

studies comparing multiagent chemotherapy to melphalan or melphalan plus prednisone.²⁶⁴ The VAD regimen as originally used for patients in relapse has more recently been tested as an "up-front" combination for previously untreated patients in a large randomized trial and has proven to be as active as other multiagent regimens in terms of frequency of remission and overall survival.²⁶⁶ However, VAD appears to induce remissions more rapidly than other regimens so that most patients who achieve remission will do so after three to four courses of therapy. Because of the rapidity of response and relatively mild myelotoxicity, it is often used for remission induction before an effort to consolidate remission with high-dose chemotherapy (see later). A summary of results from these studies appears in Table 45.4-11.

Other multicenter randomized trials using VMCP-VBAP or variants of the M2 protocol (VBMCP) failed to show better results than simpler regimens (Table 45.4-12).²⁷¹ Comparison of the different trials is difficult because of different prognostic factors, differences in the treatments used, and differences in dose modifications and other factors. Several studies compared sequential administration of various alkylating agents with simultaneous combinations or MP (data not shown). These studies showed inferiority or no advantage for the sequential regimens.^{202,270}

Although there are discrepancies between multiagent and simpler regimens in various trials, none of these regimens is curative or controls the disease for 4 years or longer. Therefore, newer therapeutic approaches are needed. The somewhat conflicting results comparing MP with combinations suggests that if there is a difference favoring multiagent chemotherapy, the difference is likely to be a small one. Accordingly, an overview or metaanalysis is being conducted by the Oxford Statistical Unit in which the primary data from various randomized trials will be analyzed to determine whether there is a small degree of benefit to be derived from multiagent cytotoxic chemotherapy.

GLUCOCORTICOID DOSAGE DURING REMISSION INDUCTION. A number of trials have shown that the addition of glucocorticoids to alkylating agent chemotherapy for remission induction increased the objective response rate but failed to increase overall survival. These conclusions were reached from trials evaluating a relatively low dose rate of glucocorticoid (e.g., 100 mg of prednisone or its equivalent per week, usually given as 100 mg/d for 4 days every 3 to 6 weeks. In SWOG's most recently completed large-scale randomized trial, glucocorticoid dose intensity was evaluated during induction therapy by comparing VMCP/VBAP to VMCP/VBAP and to the VAD regimen.²⁶⁶ In this study, the two arms that each had significantly higher glucocorticoid dose intensity (VAD and VMCP/VBAP) had significantly higher remission rates and longer median survivals than they did with VMCP/VBAP alone ($P < .01$), supporting the concept that glucocorticoid dose intensity is important during remission-induction therapy. Nonetheless, the median survival in these trials is rarely if ever longer than 4 years.

In the studies comparing alternating combination therapy to melphalan or MP, patients had a statistically significant improvement in survival with alternating combination chemotherapy. Response criteria varied between SWOG and the MRC groups but were consistent within each group's trial. In the most recent SWOG trial (which did not include melphalan or MP arms), increased glucocorticoid dose intensity improved both the response rate and median survival.

STUDIES OF INTERFERON- α ALONE OR IN COMBINATION THERAPY FOR REMISSION INDUCTION. Although IFN- α is known to have some activity in myeloma patients in relapse, the recombinant forms of IFN- α have had only limited study in previously untreated patients. In an initial report, 7 of 14 patients with previously untreated myeloma with stages I or II myeloma responded to treatment.²⁴⁸ The response was

TABLE 45.4-10. Dosage Schedules for the M2, VMCP-VBAP, ABCM, and VAD Regimens

Drug Regimen*	Vincristine	Melphalan	Cyclophosphamide	Carmustine	Doxorubicin	Glucocorticoid
M2 regimen ²⁶²	0.03 mg/kg d 1	0.25 mg/kg d 1-7	10 mg/kg d 1	0.5 mg/kg d 1	—	1 mg/kg d 1-7
VMCP ²⁰⁴	1 mg d 1	6 mg/m ² /d d 1-4	125 mg/m ² /d	—	—	Pred 60 mg/m ² /d d 1-4
VBAP ²⁰⁴	1 mg d 1	—	—	30 mg/m ² d 1	30 mg/m ² d 1	—
ABCM ²⁶⁴	—	6 mg/m ² /d d 1-4	100 mg/m ² /d d 1-4	30 mg/m ² d 1	30 mg/m ² d 1	Pred d 1-4
VAD ²⁶⁵	0.2 mg/m ² /d d 1-4 CI	—	—	—	9 mg/m ² d 1-4 CI	Dex 40 mg/d days 1-4, 9-12, and 19-22

P, prednisone; D, dexamethasone.

* As currently used, the M2 protocol is usually repeated at 4- or 5-week intervals. The VMCP-VBAP program repeats courses of chemotherapy in 21-day cycles using either a direct alternation of the two regimens or a synopated alternation wherein VMCP is used for three cycles followed by VBAP for three cycles with similar therapeutic results by either of these schedules. Currently, an every-3-week alternation is used. The MRC has used an almost identical schedule to VMCP-VBAP in their alternating program, except that vincristine and prednisone have been deleted. Alternations are also at 3-week intervals in the MRC's ABCM program. The VAD regimen is repeated every 35 days, and patients generally receive an anti-infective agent (e.g., sulfa trimethoprim or ciprofloxacin) during the period of blood count nadir (e.g., days 10 to 20), as well as an H₂-blocking agent.

TABLE 45.4-11. Results of Alternating Combination Chemotherapy Regimens Use for Remission Induction in Multiple Myeloma in Selected Multicenter Randomized Trials

<i>Investigation*</i>	<i>Treatment</i>	<i>Patients</i>	<i>Response Rate (%)†</i>	<i>Median Survival (mo)</i>
SWOG ALTERNATING COMBINATIONS VS MP OR VCP				
Study 7704 ^{204,269}	VMCP + VABP + VCAP	160	54	42
	MP	77	32	23
Study 7927 ²⁶⁹	VMCP + VBAP	93	54	48
	VCP	107	28	29
MRC ALTERNATING COMBINATION VS MELPHALAN				
Myelomatosis ²⁶⁴	ABCM	314	61	32
	Melphalan	316	59	24
SWOG COMPARISON OF GLUCOCORTICOID DOSE INTENSITY²⁶⁸				
	VMCP/VBAP	169	36	31
	VMCPP/VBAPP	171	49	40
	VAD	169	50	35

* In these studies, patients had a statistically significant improvement in survival with alternating combination chemotherapy as compared with melphalan or MP therapy.

† Response criteria varied between SWOG and the MRC groups but were consistent within each groups' trial.

TABLE 45.4-12. Results With Combination Chemotherapy Regimens Used for Remission Induction in Multiple Myeloma in Multicenter Randomized Trials That Failed to Show a Survival Advantage With Multiagent Chemotherapy Compared With Simple Alkylating Agent Regimens

<i>Investigations</i>	<i>Treatment</i>	<i>Patients</i>	<i>Response Rate (%)</i>	<i>Median Survival (mo)</i>
Argentine ²⁷³	MeCCMVP	105	46	41
	MP	129	38	39
CALGB ²⁷²	MCBP (I.V.)	156	56	29
	MCBPA (I.V.)	157	44	26
	MP (I.V.)	146	47	33
Canadian ²⁰³	MCBP	116	47*	31
	MP	125	31*	28
Danish ²⁶⁸	M2	31	45	21
	VMP	32	73	30
	MP	33	58	21
ECOG ²⁷⁴	M2	134	74	~31
	MP	131	53	~30
Finnish ²⁷⁵	MOCCA	64	75	41
	MP	66	54	45
Norwegian ²⁷⁶	M2	33	74	33
	MP	34	67	33
SECSG ²⁷⁴	BCP	186	49	36
	MP	187	52	36
Italian ²⁷¹	VMCP-VBAP	158	77	32
	MP	146	64	37

MeC, methyl-CCNU; B, BCNU, (carmustine); C, cyclophosphamide; V, vincristine; P, prednisone; A, doxorubicin (adriamycin); MOCCA, melphalan, vincristine, CCNU, cyclophosphamide, doxorubicin.

* SWOG response criteria (all others reported by Myeloma Task Force Criteria).

associated with an increase in residual polyclonal immunoglobulins. However, two randomized trials comparing initial therapy with IFN- α to chemotherapy have shown IFN- α monotherapy to be less active than standard chemotherapy.^{277,278} Recombinant IFN- α has also been integrated into combination chemotherapy with alkylating agent and prednisone combinations.²⁴⁹ On the basis of the initial experience with this approach, the CALGB initiated a randomized trial comparing the effectiveness of MP to MP plus recombinant IFN- α .²⁷⁹ This study, as well as that by the Myeloma Group of Central Sweden,²⁸⁰ failed to show overall benefit from the addition of IFN- α to melphalan-prednisone. Several more recent trials have also failed to show significant overall survival benefit in myeloma by adding IFN to commonly used multiagent induction chemotherapy regimens. A trial conducted by ECOG evaluated the addition of IFN- α 2 or high-dose cyclophosphamide to the VBMCP regimen as compared with VBMCP. Although this large, randomized trial reported a higher "complete remission" rate with the IFN-containing combination compared with VBMCP alone (17% versus 10%), there was no difference in overall response or survival compared with the other induction regimens tested.²⁸¹ An additional recent randomized trial conducted in France²⁸² using the VMCP/VBAP regimen with or without IFN- α also failed to show any benefit from the addition of IFN.

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL RESCUE. For more than a decade, it has been clear that use of high-dose chemotherapy (e.g., with intravenous melphalan at 2 to 3 times the normal dosage range) either used alone or with autologous hematopoietic stem cell rescue could improve the apparent "complete remission" rate for patients with multiple myeloma in relapse.²⁸³ Such results have been obtained at the cost of the substantial toxicity associated with severe bone marrow aplasia, which routinely occurs after high-dose chemotherapy. A number of single institutions and groups since conducted studies of high-dose chemotherapy with melphalan or other agents along with the use of hematopoietic growth factors and autologous hematopoietic stem cell rescue with peripheral blood stem cells (PBSC) or bone marrow stem cells (BMSC) or the combination for previously untreated patients with myeloma. Use of hematopoietic growth factors plus stem cells in general permits higher doses to be administered than with high-dose chemotherapy alone, and shortens the time required for recovery of bone marrow function after chemotherapy-induced marrow aplasia. These programs were initiated after it was determined that, in refractory patients, high-dose chemotherapy with autologous stem cell rescue could be initiated with a relatively low mortality rate associated with the procedure.²⁸⁴⁻²⁸⁸ A variety of regimens have been used in such high-dose chemotherapy efforts. In general, patients are first brought into at least a partial remission with combination chemotherapy (e.g., VAD), after which hematopoietic stem cells are collected for subsequent engraftment. It is not clear whether tumor cell contamination of the autograft is more significant when PBSCs or BMSCs are utilized, although most groups now prefer the use of PBSCs that are obtained and cryopreserved from leukopheresis collections after stem cell mobilization with high doses of cyclophosphamide and growth factor priming with either recombinant human granulocyte-monocyte colony-stimulating factor or recombinant

human granulocyte colony-stimulating factor. In vitro techniques to enrich the graft for CD34+ hematopoietic stem cells as well as incubation of the cell suspension with antitumor drugs or monoclonal antibodies or both have been used to deplete the autograft of contaminating myeloma cells.²⁸⁹ Before performing the autologous transplant, the patient receives a "conditioning regimen" such as high-dose melphalan (e.g., 140 mg/m² to 180 mg/m²) either alone or combined with total body irradiation (e.g., 10 Gy).

The interested reader should review specific research protocols and referenced articles for the details of specific high-dose chemotherapy protocols because there are significant differences from protocol to protocol for autologous transplantation in myeloma. If such therapy is to be used, it should be administered at identified centers of excellence for bone marrow transplantation that have adequate personnel and support resources available. Most patients receiving an autograft after high-dose chemotherapy are placed on some form of maintenance treatment (e.g., IFN) because relapse from complete remission can occur relatively rapidly even with high-dose chemotherapy. At present, there is no evidence to suggest that high-dose chemotherapy with autologous stem cell rescue is a curative procedure. Accordingly, it is necessary to critically compare toxicity, response, and survival duration outcomes with autologous transplants against more conventional dose chemotherapy approaches. The recent results of a randomized study by the French Myeloma Intergroup have suggested that response rate, event-free survival and overall survival after high-dose chemotherapy for previously untreated myeloma are superior to those achieved with conventional combination chemotherapy,²⁹⁰ (Fig. 45.4-9). A very large intergroup study is now underway in the United States and Canada (SWOG, ECOG, CALGB, and NCI-Canada) to definitively answer the question of whether early use of high-dose chemotherapy with an autologous transplant is superior to conventional chemotherapy. Patients on the conventional chemotherapy arm may have PBSCs stored after VAD induction therapy (as is the case on the high-dose chemotherapy arm) with the potential that they may be able to receive a "late transplant" (at relapse) on the conventional dosage arm. Therefore, this study will address the issue of early versus late use of high-dose chemotherapy and stem cell transplantation in myeloma. In general, because of toxicity, high-dose chemotherapy/autologous transplantation programs are restricted to patients under age 65 who show a favorable response to initial chemotherapy. Patients with other adverse factors (e.g., very high serum creatinine) are often also excluded. Because age 65 is close to the median age at diagnosis (which usually ranges from 62 to 67 years in various countries), the high-dose approach is currently something that can be considered for somewhat less than half of all newly diagnosed myeloma patients. Even within this subset of patients, it will be important to evaluate relative efficacy, toxicity, and quality of life achieved with conventional versus high-dose chemotherapy with autologous stem cell rescue.

ALLOGENEIC BONE MARROW TRANSPLANTATION. Bone marrow transplantation (BMT) from a histocompatible donor has proven to be an effective means to achieve long-term disease control or cure in patients under age 55 with some forms of leukemia who have a histocompatible donor available.^{291,292}

One of the potential benefits of allogeneic transplants above and beyond just the high-dose therapy and stem cell rescue is the "allogeneic effect," which for certain neoplasms may include a "graft-versus-tumor reaction" in which donor lymphoid cells seek out and destroy residual tumor cells.^{293,294} Additionally, an allogeneic graft from a healthy donor does not have contaminating tumor cells. In one interesting anecdote, a healthy sibling donor was immunized with the myeloma immunoglobulin before bone marrow harvest for allogeneic BMT.²⁹⁵ Subsequent to the BMT, it was possible to recover from the recipient CD4+ donor T cells with specificity for the myeloma idiotype. Follow-up is inadequate to determine whether the induction of donor immunity to the myeloma idiotype will potentiate the graft-versus-myeloma effect. Although only a minority of patients with myeloma fulfill current criteria for allografting, this is nonetheless a procedure worthy of evaluation in formal clinical trials involving suitable patients referred to recognized centers for BMT.²⁹⁶ As with autografting, a variety of conditioning regimens have been used incorporating chemotherapy, total body irradiation, or both; and the reader should review primary references for specific details of these regimens. The European Registry for Blood and Bone Marrow Transplantation recently analyzed prognostic factors important for outcome after transplantation from a total of 162 myeloma patients who had allotransplants from human leukocyte antigen (HLA)-compatible siblings between 1983 and 1993 at a large number of cooperating hospitals that provided data to the registry.²⁹⁷ This report represents an update from a prior report by this group.²⁹⁸ The report includes a heterogeneous patient population including myeloma patients treated with different stages or clinical circumstances with respect to timing of BMT during the course of their disease, as well as receiving differing induction chemotherapy and differing conditioning regimens and treatments for graft-versus-host disease, etc. In this update, 44% of all patients were reported to achieve complete remission. Nonetheless,

there was a high early mortality rate with about half of the patients dying during the first year after BMT. Actuarial survival at 4 years was 32% at 4 years and 28% at 7 years. It is not clear that these survival statistics are in any way better than those achieved with combination chemotherapy, even at the longer time points (see Tables 45.4-11 and 45.4-12). Favorable factors for long-term survival included female sex, stage I disease at diagnosis (52% at 4 years), only one form of prior chemotherapy, and being in complete remission before conditioning for BMT. Patients with IgA myeloma as well as those with a serum β_2 -microglobulin of less than 4 g/L also appeared to do better after BMT. Although the time from diagnosis to transplant was not significant for survival, patients who were transplanted later than 6 months from diagnosis tended to do worse than those who were transplanted earlier. The most important posttransplant factor was the achievement of a complete remission. The most important adverse factor was the development of grade III or IV graft-versus-host disease, which was associated with poor survival.^{296,297} The results reported with allogeneic BMT for stage I patients appear to be inferior to reported results of standard chemotherapy, for which the median survival for stage I myeloma is in the range of 7 years. In general, follow-up is insufficient to determine whether outcome is better with BMT than with more conservative therapy and whether patients receiving BMT for myeloma can be cured with this procedure as they can be with chronic myeloid leukemia. A major issue for stage I patients is whether any therapy should be employed until clear evidence of symptomatic disease progression occurs. Application of additional prognostic factors, such as the proliferative index of myeloma cells or expression or lack of expression of oncogenes or tumor suppressor genes, may assist in better identifying the patient groups most likely to benefit from aggressive systemic therapies, including BMT. Development of improved methods for prevention or treatment of graft-versus-host disease as well as development of methods to permit transplanta-

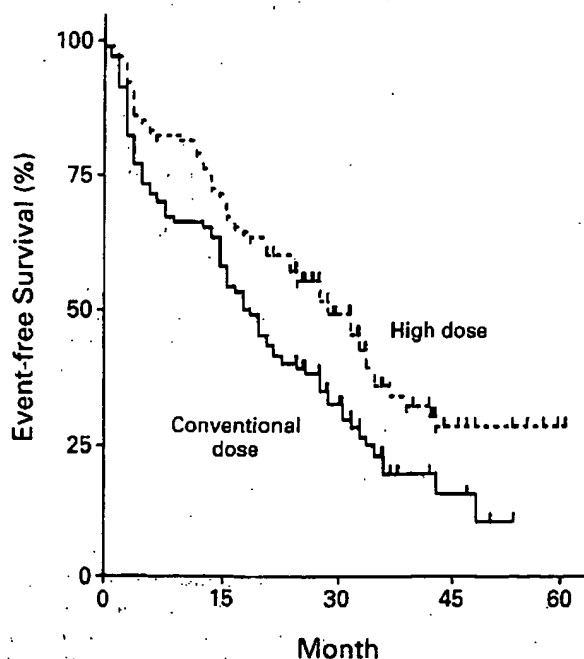


FIGURE 45.4-9. Event-free survival according to treatment group. The numbers shown below the time points are probabilities of event-free survival (the percentages of patients surviving event-free) and 95 percent confidence intervals. (Attal M, Harousseau JL, Stoppa AM, et al. A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996; 335:91)

tion in older patients will be required before BMT can have a major quantitative impact on the more general population of myeloma patients.

TUMOR CELL REDUCTION WITH INDUCTION CHEMOTHERAPY. The magnitude of tumor cell reduction with standard chemotherapy can be assessed using the quantitative methods to determine response in terms of the degree of cytoreduction achieved. For myeloma, this was first achieved using a computer-based method in which serial measurements of the amount of M-component produced per cell in vitro, intravascular mass of M-components, and catabolic rate were integrated.^{2,181} For the current standard treatment programs and magnitude of cell death determined from M-component-derived measurements, the maximum degree of cytoreduction in total tumor burden observed in patients treated with conventional chemotherapy rarely exceeds 90% to 99%. Despite continued treatment, the tumor burden appears to plateau in most cases.¹⁸¹ Kinetic analysis of the plateau-phase population suggests that the residual tumor cells behave differently from those present before treatment, and they are comparatively hypoproliferative and perhaps less responsive to cytotoxic chemotherapy.²²³ Somewhat greater degrees of cytoreduction are achieved with high-dose chemotherapy and stem cell rescue (e.g., 3 to 5 logs), but in most instances, immunofixation will reveal the presence of a residual M-component even though it is not detectable with quantitative methods. Nonetheless, as assessed with the polymerase chain reaction, some true complete remissions are achieved after high-dose chemotherapy or allografting or both. In such cases, the marrow appears normal and the M-component is not detectable nor are immunoglobulin gene rearrangements observed in circulating blood lymphocytes or bone marrow cells.

With a total tumor burden in most patients in the range of 10^{12} myeloma cells or more, it is not surprising that there is not a strong correlation between the exact magnitude of cytoreduction (e.g., 75%, 90%, 99%) and overall survival. Remission duration after induction chemotherapy can vary substantially in comparably staged patients with similar degrees of apparent cytoreduction and the presence of a clearly measurable residual M-component peak in the serum. Although the median duration of unmaintained remission is in the range of 11 months, unmaintained remissions after induction chemotherapy in some patients with stage III myeloma may last for 5 years or longer.^{299,300} This suggests that there is an alteration in the residual myeloma cell population or in the tumor-host relation. Such observations provide the basis for seriously questioning whether the residual cell mass determined from M-component levels in remission reflects the initial population of malignant plasma cells or a less malignant population more akin to that in patients with MGUS. However, patients regularly relapse with overt myeloma from unmaintained remissions, indicating that an underlying highly malignant monoclonal persists but may be hidden within a population of less highly proliferative M-component-secreting cells.

Analysis of the myeloma regrowth rate based on M-component doubling times has been carried out for patients studied sequentially after a series of unmaintained remissions.¹⁸⁰ Even in the presence of continued chemosensitivity (as reflected by cytoreduction after reinstitution of chemotherapy), some patients studied developed a progressive shortening of the M-component doubling time during subsequent unmaintained

remissions. Such observations suggest progressive loss of growth control with the emergence of a kinetically more aggressive tumor cell population.

Remission Maintenance Versus Unmaintained Remission

Therapeutic approaches in myeloma have usually been developed in a fashion analogous to those for other advanced neoplasms and have included remission-induction phase and remission-maintenance phase treatments. Myeloma patients who exhibit drug sensitivity and achieve remission usually have been maintained on a similar form of chemotherapy until the time of relapse.

The usefulness of maintenance therapy with cytotoxic drugs has been examined in several studies with similar results.^{299,301-303} Patients achieving remission with chemotherapy were randomized to maintenance chemotherapy with MP or to no maintenance therapy. Patients randomized to no maintenance received alkylating agent chemotherapy again at the earliest evidence of relapse as manifested by a rise in M-component levels or recurrent symptoms and signs of active myeloma. There was no overall survival advantage for patients receiving maintenance chemotherapy. Continuation of conventional alkylating agent therapy for patients achieving remission appears to offer no obvious advantage over unmaintained remission, as long as patients are followed closely and have treatment reinstituted when there is laboratory or clinical evidence of reactivation of myeloma. In general, patients followed in unmaintained remission should be followed monthly, with regular monitoring of serum and urine M-components to detect the first signs of relapse. Patients presenting initially with stage III myeloma with heavy Bence Jones proteinuria or amyloidosis must be followed closely, because fulminant relapse from unmaintained remission can lead to irreversible complications unless treatment is reinstituted promptly at the first sign of disease reactivation.

An approach to remission maintenance that used recombinant IFN- α was reported by the Italian Multiple Myeloma Study Group.^{304,305} In this study, 70 patients with remissions induced with MP or VMCP-VBAP (on a randomized induction) were rerandomized to maintenance therapy with recombinant IFN- $\alpha 2$ or to no treatment. The IFN- $\alpha 2$ was administered at a dosage of 3×10^6 IU/m² subcutaneously three times weekly. After 27 months of follow-up, 8 (24%) of 33 of evaluable patients receiving IFN- $\alpha 2$ and 22 (59%) of 37 patients with no maintenance had relapsed, with a significant difference ($P < .01$) in the actuarial curves of remission duration in the two groups.³⁰⁵ A larger study of IFN maintenance conducted by the SWOG with approximately 200 patients randomized to IFN maintenance or observation using 3×10^6 of IFN- α given intravenously with the same schedule showed no advantage of IFN- $\alpha 2$ over unmaintained remission for remission duration or survival (Fig. 45.4-10). A number of additional IFN- α studies for remission maintenance have subsequently been performed and none of these large-scale studies has shown an improvement in overall survival, although several suggest an increase in the time from start of maintenance to relapse.^{306,307} However, given that IFN- α has significant side effects and expense associated with its use, there is currently no consensus regarding its use as a single agent for myeloma maintenance therapy.

dose (400 to 1500 cGy) versus multiple moderate dose (2000 to 4000 cGy) programs have shown remarkably little difference.^{82,83} These studies show that there is no consistent dose-response relationship governing pain relief following the irradiation of bone metastases. The heterogeneous nature of patients studied, however, and differences in posttreatment survival times may mask such a relationship.

Some authorities continue to recommend higher doses and longer courses to palliate bone metastases. The effectiveness of high-dose therapy is supported by Archangeli and Micheli, who reported that doses of more than 4000 cGy effected a higher complete response rate.⁸⁴ Therefore, patients with a long projected survival and good performance status may be best treated by full dose (more than 4000 cGy) with conventional fractionation. When expected survival is short, high-dose or long-duration therapy is not appropriate treatment because symptoms from recurrent local tumor are rarely a problem. Cost and utilization of radiation facilities exceed the marginal benefit of high-dose therapy. Additional treatments can be considered if there is a relapse following initial low-dose therapy in these patients.

Preliminary studies looking at single-dose radiation show response rates in the 40% to 50% range.⁸¹ Complete responses were infrequent. Most patients relapsed, requiring subsequent treatment to the irradiated site. Single doses of radiation that produce equivalent short-term morbidity to standard fractionation schemes will cause more severe long-term problems. Thus, patients receiving radiotherapy for palliation of symptoms of end-stage metastatic disease are best suited for single-dose regimens. Future improvement in our understanding of bone pain will allow irradiation to be used synergistically to control local factors in the pain cascade.

Patients with disseminated bone metastases are candidates for hemibody radiation.⁸³ This is an alternative for the patients for whom localized treatment would be inadequate and effective systemic therapy is lacking. It is a pragmatic approach that eliminates the need for daily trips to the hospital over an extended period of time. The usual scheme includes administration of 600 to 800 cGy to either the upper middle or lower sections of the body. Pretreatment hydration, antiemetic, and corticosteroid therapy are important for upper body irradiation. These measures are often useful for midbody therapy as well. Toxicity is tolerable; severe or life-threatening (National Cancer Institute grade 3 or 4) toxicity was less common in the lower body and midbody regions. Salazar reported significant complications of nausea (2%), vomiting (6%), and diarrhea (8%) in these groups.⁸⁵ Complications were more frequent after upper body treatment. Grade 3 or 4 toxicity occurred due to vomiting (15%), fever (4%), and hematologic dysfunction (32%) in patients. As expected, hematologic complications were worse in patients who had undergone aggressive chemotherapy.⁸⁵ Prostate cancer appears particularly appropriate for this form of therapy. Palliation of pain was persistent until death in 82% of upper body and 67% of lower body patients. As Zelefsky and colleagues reported, hemibody radiation yields more durable pain relief than standard fractionation without any greater complications.⁷⁰

SYSTEMIC RADIONUCLIDES

Systemic administration of radionuclides can be very effective in treating symptomatic bone metastases. The approach is ap-

pealing compared with any other local or systemic therapy. It treats all involved sites rapidly and selectively. This reduces toxicity and enhances the therapeutic ratio.⁷⁸ Strategies include using a carrier that seeks the tumor or a vehicle that localizes in bone matrix. Iodine ¹³¹I is the prototype, localizing within the well-differentiated thyroid carcinoma cells. The antineoplastic effect both relieves pain and allows for healing of the underlying bone lesion. High response rates are seen with this treatment particularly early in the course of the disease. Small lesions respond better than bulk disease. Success has been achieved in up to 74% of patients with nodal metastases when sufficient radiation dose is administered (8500 cGy).⁸⁶ Bony deposits of thyroid cancer may be the least responsive site; and dosimetry is not so well defined. Proye reported that 17% of ¹³¹I active bone lesions and only 7% of all bone lesions responded to therapy.⁸⁷ Lesions that do not respond to ¹³¹I can then be treated successfully by external beam radiation with little extra toxicity.

Bone-seeking isotopes such as ⁸⁹Sr are advocated for a variety of primary cancer histologies.^{88,89} These agents localize in the mineral of bone. Actively calcifying areas concentrate most of the isotope, just as with radionuclide scintigraphy. Degradation of the isotope in the host bone administers local short-acting radiation to the adjacent tumor cells. The low-energy β emission ⁸⁹Sr is safer and better tolerated than high-energy isotopes such as ³²P-orthophosphate and others. All agents cause bone marrow suppression. Again, it is worse in heavily pretreated patients undergoing chemotherapy.

⁸⁹Sr has very good response rates ranging from 51 to 91%. Although bone marrow toxicity occurs, it is less than after treatment with other radionuclides. New isotopes such as ¹⁸⁵Rh and other isotopes with short half-lives have interesting properties. They emit both γ rays permitting imaging of blastic tumors in particular and β particles that confer therapeutic value. As in studies of other radioactive agents and radiation modalities, response rates have been reported to be in the 65% to 85% range.⁸⁹ Two large trials have recently compared ⁸⁹Sr with external beam conventional and single-dose regimens.^{90,91} The UK Mastastron Investigator's Group study included 284 protocol-treated patients. Survival, overall, and dramatic pain relief were indistinguishable between the groups. However, ⁸⁹Sr patients had fewer and less severe new symptomatic lesions.⁹⁰ These results suggest that a strategy of systemic radionuclide administration may be complemented by local external beam radiotherapy to achieve the optimal palliation of symptoms in patients with metastatic bone disease.

BISPHOSPHONATES

New-generation bisphosphonates may actually prevent the development of bony metastases. In several animal models, injected tumor cells failed to establish colonies in bone that had received pretreatment by bisphosphonate.^{92,93} Conceivably, this could translate into the clinical situation. For tumors with certain histologic or molecular features, bisphosphonates could even be considered while treating the primary tumor. A more conventional mode is to use the bisphosphonates to treat hypercalcemia, stop bone reabsorption, and reduce pain from established bone metastases. Several studies have demonstrated significant reductions in "bone events" (new bone le-

sions, increase in bone pain hypercalcemia, or pathologic fracture) in breast cancer patients as well as in other patients with bone metastases. This translates into real benefit: improving quality of life as well as treating any episodes of hypercalcemia that may occur in these patients. Repetitive treatment every 1 to 3 weeks on an outpatient basis is often required to maintain tumor control. The bisphosphonates do not have a cytotoxic effect, nor do they interfere with other commonly used chemotherapeutic agents. The independent mechanism of action makes bisphosphonate therapy an attractive adjunct to other modes of treatment.^{94,95}

IMPENDING FRACTURES: PROPHYLACTIC FIXATION

There is no clear definition of impending fracture. The indications for operative treatment of impending fractures are controversial and waiting for refinement. At Memorial Sloan-Kettering Cancer Center, a functional system has been employed that has practical implications.^{17,35,96,97} In each of the following four circumstances, major bone loss has usually been encountered surgically and the bone was found to be essentially fractured:

- A painful medullary lytic lesion occupying more than 50% of the cross-sectional bone diameter
- A painful lytic lesion involving the cortex greater than the cross-sectional diameter of the bone
- A painful cortical lesion more than 2.5 cm in length
- A lesion producing mechanical pain after radiation therapy

Keene evaluated the clinical and radiographic risk factors in an attempt to predict pathologic fracture of the femur.⁹⁸ This study, the largest to date, evaluated 2673 breast cancer patients who had undergone skeletal surveys. Two hundred three patients had evaluable proximal femoral metastases. Only 11% of such patients sustained a pathologic fracture. There was no difference in the patient demographics, pain pattern, or radiation response between the fracture and the no-fracture patients. The lesion size did not predict fracture occurrence dependably. There was the same extent of bone involvement in the lesions that fractured as in the ones that did not. The authors found no criteria to identify the bone at risk for fracture. They concluded that plain radiographic measurements are insufficient to identify the high-risk lesion. The study was limited to the single anteroposterior radiographic evaluation present in the skeletal survey.

The scientific foundation for predicting fracture risk has been improved and recently summarized by Callaway and Healey.⁹⁹ Computer modeling of the proximal femur in vitro testing has allowed McBroom and associates^{96,100} and Beaupre¹⁰¹ to predict femoral strength more accurately. Evaluating intertrochanteric and subtrochanteric lesions subject to bending forces, they found that endosteal reabsorption of one-half the cortical width weakens the bone by 70% and leaves the patient at high fracture risk. Unfortunately, similar analysis is not available for other anatomic sites. Mirels and associates have proposed a graduated scoring system that further refines the Memorial Hospital and Harrington crite-

ria.¹⁰² They include clinical and radiographic factors to generate a composite score from 0 to 12 that correlates with fracture risks. Four factors were each evaluated on a 0 to 3 scale: anatomic site, pain pattern, radiographic nature, and lesion size¹⁰² (Table 50.4-1). The table is a scoring system to predict pathologic fracture.

Mirels and associates investigated 78 lesions followed over the course of 6 months. Fifty-one lesions did and 27 did not fracture. There was a mean score of 7 for the nonfracture patients versus 10 for the fracture patients. Fracture risk paralleled an increase in the score above, but there was significant overlap between the groups. Follow-up beyond the 6-month study period was also lacking. The incidence of late failure and the necessity for additional treatment were not discussed. The authors concluded that the lesions scoring below 7 could be irradiated, whereas those with a higher score should be treated by internal fixation and postoperative irradiation.

Subset analysis was provocative. Increases in scores from 9 to 10 were associated with a 2.5-fold increase in fracture rate up to 80%. This dramatic difference in clinical outcome based on a single point difference in the evaluation score is worrisome and negates some of the value of this system. The nonparametric and subjective nature of the evaluation is also problematic.

Equally valuable is the ability of this scoring system to predict which lesions would not fracture. The fracture rate was small (5%) when the lesion was less than two thirds of the bone diameter, but it increased to 81% for lesions larger than two thirds the shaft diameter. They stressed that standard radiographs are inadequate to grade many lesions and recommended the use of CT scan to improve diagnostic accuracy. Mirels also emphasized the important distinction between pain and "functional" pain. The functional or mechanical pain was that which worsened with weight-bearing. It reflects structural insufficiency and was the most significant indicator of bone failure, enjoying almost universal success in predicting fracture. Lesions measuring greater than twice the bone diameter were associated with mechanical, functional pain. Fracture probability in patients with smaller lesions was only 10%.

TABLE 50.4-1. Scoring System to Predict Pathologic Fracture

Variable	Points		
	1	2	3
Site	Upper extremity	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Mechanical
Radiograph	Blastic	Mixed	Lytic
Size (% of Shaft)	0-33	34-67	68-100
Score	Patients		Fracture Rate (%)
0-6	11		0
7	19		5
8	12		33
9	7		57
10-12	18		100

Radiation involving the pelvis or spine is particularly problematic because of the large volume of marrow in those bones.

Clinical Trials With Erythropoietin

Use of EPO in anemia associated with cancer has been extensively investigated.⁶²⁻⁶⁴ Trials have been conducted in patients with anemia due to marrow involvement with lymphoproliferative disorders⁶⁵; myelodysplastic syndromes, or solid tumors; and in patients developing anemia after chemotherapy,⁶⁶⁻⁶⁸ autologous transplantation,⁶⁹ allogeneic transplantation,⁷⁰ or irradiation therapy⁷¹, and in patients with anemia of cancer. Responses, generally defined as an increase in hemoglobin or a decrease in transfusion requirements, are quite high in most groups of patients, typically in the area of 50%.^{68,72-75} Lack of response correlates with high pretreatment serum level of endogenous erythropoietin. Response has been associated with improved performance status and quality of life.⁷⁶ However, despite the high response rate and the apparent reduction in transfusions, EPO therapy is expensive, and additional cost-benefit studies are needed.⁷⁷

Clinical Pharmacology of Erythropoietin in Cancer Patients

The ideal dose and schedule of EPO for treating anemia of cancer or anemia of chronic disease (excluding chronic renal disease) are not yet known, although some general comments can be made. Subcutaneous administration three times weekly appears to be at least as effective as daily intravenous administration. Higher doses are not clearly better than lower doses, but there is a threshold effect, and intravenous doses less than 100 U/kg and subcutaneous doses less than 50 U/kg may be associated with lower response rates. A reasonable approach would be 50 to 100 U/kg three times weekly by subcutaneous injection, which could be increased to 300 U/kg after 6 weeks without response. Late responses are fairly common, and 9 weeks of therapy or more may be required in some responding patients. Since many patients fail to respond even to higher levels of EPO, there has been considerable interest in predicting early in the course of treatment who is likely not to respond. Several algorithms have been generated and suggest that failure to increase hemoglobin by more than 0.5 g/dL or serum ferritin more than 400 ng/mL after 2 weeks of treatment predict for failure.⁷⁸ Iron deficiency will prevent response to erythropoietin and should be considered in selected nonresponsive patients.⁷⁹ Finally, most studies so far have involved concurrent administration of EPO with chemotherapy or radiation. Other schedules where EPO is given before or at the end of chemotherapy are being investigated.

Cisplatin-Associated Anemia

Approximately 40% of patients receiving cisplatin chemotherapy develop anemia and many will require transfusion. Studies of EPO administration to treat cisplatin-induced anemia have generally been positive, even in elderly patients.^{73,74,80} Henry and Abels⁶⁸ performed three randomized double-blind, placebo controlled trials of EPO for anemic cancer patients not receiving concomitant chemotherapy, patients receiving chemotherapy that did not include cisplatin, and patients receiving cisplatin-containing chemotherapy. Patients not on

chemotherapy received 100 U/kg three times weekly, whereas those on chemotherapy received 150 U/kg three times weekly. Overall, the trials involved 413 patients. Patients receiving EPO in all three trials had a statistically significant increase in hematocrit compared with placebo-treated patients.⁶⁸ Quality of life improved significantly for EPO-treated patients with an overall response rate of about 50% in all three groups. Similar results were reported by Cascinu and coworkers,⁶⁶ who performed a randomized, double-blind trial with EPO versus placebo in 100 patients with cisplatin-associated anemia (hemoglobin less than 90 g/dL), administering EPO at 100 U/kg subcutaneously three times per week. After 9 weeks of therapy, the mean hemoglobin level of the EPO treated group was statistically different from placebo patients (EPO patients went from a baseline of 8.6 ± 0.6 to 10.5 ± 0.9 g/dL at 9 weeks, whereas placebo patients went from a baseline of 8.7 ± 0.5 to 8.1 ± 1.1 g/dL at 9 weeks). Also, only 20% of EPO-treated patients required blood transfusion versus 56% of placebo-treated patients. No significant side effects of EPO treatment were encountered. Another multicenter, double-blind, placebo controlled trial was conducted by Case and coworkers,⁶⁷ who randomized 153 anemic cancer patients receiving cyclic chemotherapy to EPO, 150 U/kg three times weekly, or placebo. EPO-treated patients had a statistically significant increase in hematocrit and a trend toward lower transfusion requirements. Again, no significant side effects were encountered. Overall, these multiple, randomized, controlled trials indicate that EPO is safe and effective for therapy of both chemotherapy-associated and non-chemotherapy-associated chronic anemias in patients with solid tumors. Treatment reduces need for transfusion and improves quality of life for many patients.

Anemias Associated With Myelodysplastic Syndromes

The role of EPO in treating anemia associated with hematologic malignancies is somewhat less clear, particularly for the anemia of myelodysplastic syndromes (MDS). Most studies reported to date are uncontrolled and have included only small numbers of patients.⁸¹⁻⁸⁸ The response rates tend to be less than 25%, although a few patients will respond to higher doses of EPO.⁸⁹ A recent metaanalysis of 205 patients with MDS from 17 different studies found an overall response rate of only 16%, with a particularly low response rate in patients with refractory anemia with ringed sideroblasts (RARS, 7.5% response rate). Factors which predicted for a low response rate were transfusion dependence, high serum erythropoietin, and RARS. Several studies have looked at sequential or combined use of a myeloid growth factor with erythropoietin,⁸⁹⁻⁹² but responses are not clearly higher with the doses and schedules studied so far. As is the case for the anemia of cancer, late erythropoietin responses may be observed,⁹³ making long courses of therapy necessary in clinical trials. At the present time, erythropoietin appears to benefit only a small number of patients with MDS, primarily patients with low serum erythropoietin levels and minimal transfusion requirement. Additional clinical trials that include cost-benefit analyses are needed in MDS.

Use of Erythropoietin in Bone Marrow Transplantation

EPO treatment has not proved to be useful so far for treatment of anemia associated with bone marrow transplanta-

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tion.^{69,70,94-96} Three randomized, controlled studies have examined erythropoietin versus placebo after autologous or allogeneic transplantation.^{70,94,97} Biggs and coworkers gave erythropoietin (300 U/kg IV three times weekly) or placebo to 91 patients undergoing allotransplantation. There was no reduction in red blood cell or platelet transfusion requirement and no reduction in hospital stay.⁷⁰ Link and colleagues randomized 107 patients undergoing allotransplantation to erythropoietin (150 U/kg/d by continuous intravenous infusion) or placebo until patients reached 7 days of transfusion independence or day 41.⁹⁷ The time to transfusion independence was reduced by erythropoietin from 27 to 19 days, but the number of transfusions required in the peritransplant period was similar. Erythropoietin-treated patients had a somewhat smaller transfusion requirement from days 42 to 100. The same group conducted a randomized trial of identical design with 57 patients undergoing autologous transplantation.⁹⁷ No difference in transfusion requirement was observed. Chao and colleagues conducted a placebo controlled trial of erythropoietin (600 U/kg three times weekly) starting treatment 3 weeks before autologous bone marrow transplantation in 35 patients with lymphoma.⁹⁴ All patients also received G-CSF after marrow reinfusion. No differences were observed in transfusion requirement or hematopoietic recovery. Similar results were reported when erythropoietin was combined with GM-CSF in a nonrandomized study of autologous marrow transplantation with historical controls.⁹⁵ In a novel approach, Mitus and colleagues treated both allogeneic marrow donor and recipient with erythropoietin.⁹⁸ The donors were phlebotomized a median of 6 U of blood over a 5-week period. Using this approach, 5 of 11 patients underwent transplant using only donor-derived red blood cells. However, in general terms, erythropoietin has been of only very modest benefit in the marrow transplant setting.

Overall, erythropoietin has an important role in the therapy of anemia in some cancer patients. In the individual cancer patient, the clinician needs to look carefully for treatable causes of anemia such as iron deficiency or blood loss, consider the underlying illness and other factors, such as the serum EPO level, to determine if a course of EPO treatment is warranted.

USE OF HEMATOPOIETIC GROWTH FACTORS TO REDUCE CHEMOTHERAPY-ASSOCIATED MYELOSUPPRESSION

Myelosuppression Associated With Standard Dose Chemotherapy

Neutropenia and infection are major causes of morbidity and mortality in cancer patients and are dose-limiting for many types of chemotherapy. It is standard practice to treat all neutropenic, febrile patients with broad-spectrum antibiotics, even though many patients do not have documented infections. This adversely affects quality of life, increases hospital costs, and also often results in reduction of chemotherapy doses for subsequent cycles. Reducing the incidence of febrile neutropenia and infection are major goals of CSF therapy in this setting.

G-CSF. G-CSF has been extensively investigated in clinical trials as an adjunct to cancer chemotherapy. The initial phase I-II studies in bladder cancer and small cell lung cancer patients

established that G-CSF administration by either subcutaneous or intravenous routes caused a dramatic, dose-dependent increase in blood neutrophil counts. Data from numerous phase I-II studies predicted that administration of G-CSF following standard-dose, myelosuppressive chemotherapy would shorten the duration of neutropenia, but it was not clear from these early trials if this would translate into clinical benefit. The efficacy of G-CSF has now been established in a series of randomized, controlled, clinical trials in which the chemotherapy was sufficient to cause febrile neutropenia in more than 40% of the control group. A pivotal trial was conducted by Crawford and coworkers,⁹⁹ who randomized patients with small cell lung cancer to receive G-CSF or placebo after a myelosuppressive regimen containing cyclophosphamide, doxorubicin, and etoposide (CAE). The incidence of febrile neutropenia was significantly reduced in patients receiving G-CSF. Further, length of hospital stay, incidence of confirmed infections, and days of antibiotic use were reduced by about 50%.⁹⁹ In general terms, the results of this study have been confirmed by three other randomized, controlled phase III studies: one in small cell lung cancer patients receiving CAE chemotherapy¹⁰⁰; one in which patients with non-Hodgkin's lymphoma received vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin¹⁰¹; and a third study in which patients with various types of cancer received several different chemotherapy regimens.¹⁰² In none of these randomized studies was there a clear difference in mortality, tumor response rate, or survival. Thus, despite the fact that some epithelial tumor cells express G-CSF receptors, there does not appear to be any adverse effect of G-CSF on tumor growth when given with chemotherapy. In these randomized studies, the toxicity of G-CSF was minimal and generally limited to medullary bone pain, which can usually be relieved with analgesics.

The timing of G-CSF after chemotherapy has been investigated in patients receiving melphalan (25 mg/m²).⁵³ Delaying administration to 8 days after completion of chemotherapy appeared to be somewhat less effective than immediate administration, and it is now general practice to start G-CSF 24 to 48 h after completing chemotherapy administration, typically continuing until the neutrophil count has recovered to 10,000/ μ L. However, administration of G-CSF for a defined period of only 7 days had benefit.⁵³

GM-CSF. Administration of GM-CSF after standard dose chemotherapy has also been extensively evaluated, and most studies indicate potential benefit. In phase I-II studies where GM-CSF was administered in alternate cycles, shortening of the duration of neutropenia has been observed.⁶⁰ In larger, randomized, placebo controlled studies, however, benefit has in some cases been limited to subsets of patients,¹⁰³⁻¹⁰⁵ and the ability of GM-CSF to reduce the incidence of febrile neutropenia and infection in this group of patients is somewhat less well established than for G-CSF. In preliminary results from a randomized study in patients with small cell lung cancer receiving CAE chemotherapy, for example, GM-CSF reduced the duration of neutropenia, but not the incidence of febrile neutropenia, days in hospital, or antibiotic use. Similarly, in a randomized trial of GM-CSF in patients with germ cell cancer receiving vinblastine, ifosfamide, and platinum, no significant beneficial effects were seen.¹⁰³

TABLE 54.1-15. Adjuvant Analgesics in the Management of Cancer Pain**ADJUVANT DRUGS FOR NEUROPATHIC PAIN**

Antidepressants
 Anticonvulsants
 Oral and cutaneous local anesthetics
 Corticosteroids
 Clonidine
 Benzodiazepines
 Neuroleptics
 α_2 -Adrenergic agonists
 NMDA antagonists
 Calcitonin

ADJUVANT DRUGS FOR BONE PAIN

Biphosphonates
 Gallium nitrate
 Calcitonin
 Strontium-89

ADJUVANTS TO TREAT SIDE EFFECTS

Antiemetics
 Compazine
 Metaclopramide
 Ondansetron
 Psychostimulants
 Caffeine
 Methylphenidate
 Dextroamphetamine
 Laxatives
 Senna

ADJUVANTS TO ENHANCE ANALGESIA

Acetaminophen
 NSAIDs
 Hydroxyzine

guidelines for their use, sequential drug trials are necessary to identify the most useful drug and dose titration to find a safe effective dose. Table 54.1-15 lists the commonly used adjuvants and their therapeutic categories.

ADJUVANT ANALGESICS FOR NEUROPATHIC PAIN.

The common neuropathic pain syndromes in patients with cancer include injury to peripheral nerves and plexus by tumor invasion, chemotherapy, surgery, or viral agents. Depending on the intensity of pain, nonopioid and opioid analgesics are the first-line agents. However, as previously discussed, there is evidence to suggest that such neuropathic pains are less responsive to nonopioid and opioid approaches. Some of the commonly used adjuvant drugs for managing this population of patients are described in the following paragraphs.

Antidepressants. The tricyclic antidepressants (TCAs) may be the most useful group of psychotropic drugs used in pain management.^{129,130} Their analgesic effects are mediated by enhancement of serotonin activity. Data from controlled trials indicate that both the tertiary amine TCAs (amitriptyline, doxepine, imipramine, and clomipramine) and the secondary amine compounds (desipramine and nortriptyline) have anal-

gesic effects. More recently, one of the serotonin selective reuptake inhibitors (SSRIs), paroxetine, has also been shown to have analgesic properties in patients with neuropathic pain.¹³¹ These drugs have been reported to be effective to treat both continuous dysesthesias and intermittent lancinating dysesthetic pain. The doses used for analgesia are far below those needed to produce an antidepressant effect. The analgesic properties of these drugs appear to occur independent of their mood-altering effects. Patients should be started on low doses of 10 to 25 mg and titrated up to achieve adequate analgesia in a 2- to 4-week trial. Blood levels should be measured to determine both patient compliance and drug absorption because of wide individual variation. Patients who are unable to tolerate amitriptyline, or who are predisposed to its sedative, anticholinergic, or hypotensive effects, should be considered for a trial with a secondary amine TCA or an SSRI such as paroxetine. In the management of cancer patients with pain, the antidepressant drugs are the first-line therapeutic approach for neuropathic pain, and every attempt should be made to provide the patient with a several-week trial before discontinuing these drugs.

Anticonvulsants. The role of anticonvulsants in the management of patients with neuropathic pain is based, in part, on the fact that the mode of action is to stabilize membranes and altering sodium and calcium influx.¹³² Many of these patients complain of brief paroxysmal lancinating pains. To date, clinical experience with the anticonvulsants and baclofen has been positive.¹³³ The drugs most commonly used include carbamazepine, phenytoin, valproate, clonazepam, and gabapentin. Clinical experience is greatest with carbamazepine, but the utility of this drug in the cancer population is limited by its potential to produce bone marrow suppression, particularly leukopenia. The dosing guidelines used for the treatment of seizures are suggested in managing neuropathic pain. Each of the drugs should be initiated at low doses and gradually titrated upward. Anecdotal experience suggests that using intravenous loading doses of phenytoin for patients in an acute crisis with severe lancinating pain may be of clinical value. There are no data to relate the plasma level and pain relief with any of these drugs. As previously stated, sequential trials are necessary to identify the most useful agent. With the use of baclofen, which is generally well tolerated, doses should begin at 5 mg 2 or 3 times a day with titrations upward, with the highest reported doses between 100 to 150 mg per day titrated to the individual responses of the patient.¹²⁷

Oral Local Anesthetics. The use of both brief intravenous local anesthetic infusions and maintenance oral anesthetic drugs has demonstrated some efficacy in the management of chronic neuropathic pain, particularly in those patients with both lancinating and continuous dysesthesias. Mexilitine is the oral local anesthetic for which there are pilot data to support its analgesic efficacy.¹³⁴ The initial dose of mexilitine is low, at 150 mg/d, with gradual upward dose titration. Electrocardiograms should be monitored at higher doses, and blood levels of mexilitine may be useful to prevent toxicity. Alternatively, the use of brief intravenous infusions of lidocaine may be helpful in patients who have an opioid-refractory continuous dysesthesia that has not responded to an antidepressant or anticonvulsant.¹³⁵ There are no good data available to predict what patients might respond to the use of oral local anesthetics, although data are

available for the use of brief local anesthetic infusions to determine control of cardiac arrhythmias. These drugs clearly serve as a second-line approach, with individualized therapy the rule.

Cutaneous Local Anesthetics. The use of cutaneous anesthesia has been suggested to be most helpful in patients who have significant allodynia and marked hyperesthesia. The use of the topical application of a local anesthetic such as EMLA (eutectic mixture of local anesthetics) has been demonstrated to be efficacious in patients with postherpetic neuralgia.¹³⁶ The use of high-concentration lidocaine (5% and 10%) has also been reported to be effective in this population of patients.¹³⁷ The cream should be applied under an occlusive dressing to increase skin penetration and augment analgesic efficacy.

Corticosteroids. A series of controlled and uncontrolled surveys have demonstrated the use of chronic steroid therapy to reduce pain in patients with breast and prostate cancer and to improve quality of life.¹³⁸⁻¹⁴⁰ In a controlled study of corticosteroid use in patients with far-advanced disease, transient improvement in appetite, analgesia, and mood were noted, but they were not sustained after the initial effect.¹³⁹ The major indications for corticosteroid use include refractory neuropathic pain, bone pain, pain associated with capsular expansion or duct obstruction, and headache due to increased intracranial pressure. In certain cancer pain syndromes, such as epidural cord compression, 85% of patients receiving 100 mg of dexamethasone as part of their radiation therapy protocol reported significant pain relief associated with marked reduction in analgesic requirements.¹⁴¹ Similarly, in patients with tumor infiltration of the brachial and lumbosacral plexus, steroids provided additive analgesic effects. The risk of adverse effects associated with corticosteroid therapy varies with the duration. Long-term use may be associated with GI toxicity and acute psychosis. A wide range of doses has been suggested, including doses of 30 mg/d in patients with prostate cancer, which was effective in providing improved quality of life and reduced pain. As stated, with epidural cord compression, initial doses of 100 mg with maintenance doses of 16 mg have been associated with effective analgesia. In my experience, the use of 16 mg as a loading bolus and rapid titration to lower doses of approximately 4 mg/d is one approach commonly used in the refractory chronic pain patient with advanced disease.

Other Adjuvant Drugs. A wide variety of other drugs have been used to manage neuropathic pain, including clonidine, benzodiazepines, neuroleptics, α_2 -adrenergic agonist drugs, NMDA antagonists, and peptides.^{31,127} Of the benzodiazepines, clonazepam is commonly used in patients with lancinating or paroxysmal pain.¹⁴² The use of these drugs must be balanced with their potential for somnolence and cognitive impairment. They serve as a second- to third-line therapy in patients who have not responded to antidepressant or anticonvulsant drug therapy. Of the neuroleptics, pimozide has been reported to be analgesic in patients with trigeminal neuralgia.¹⁴³ Methotrimeprazine has been demonstrated to have analgesic properties comparable to morphine.¹⁴⁴ This drug has sedative, anxiolytic, and antiemetic properties and is commonly used in patients who have excessive opioid side effects. It provides analgesia by a nonopioid mechanism. Coadministration of these drugs with opioids can often be effective in patients with neuropathic pain. Of the α_2 -adrenergic agonist

drugs, clonidine has been demonstrated to be analgesic in controlled trials.¹⁴⁵ It can be used by either the oral or transdermal route and has been reported to be specifically effective in patients with dysesthetic pain who demonstrate sympathetic hyperactivity. Dextromethorphan and ketamine are two commercially available NMDA antagonists. Both have been shown to have analgesic effects in controlled studies of experimental pain.^{146,147} The mechanism of action relates to the fact that the NMDA receptor reduces the development of the wind-up phenomenon, which occurs as a result of changes in the response of central dorsal horn neurons with neuropathic pain.¹⁴⁸ Case reports have suggested that dextromethorphan has been beneficial in selected patients, although a controlled trial of low-dose dextromethorphan is negative. The drug may be initiated at doses of 40 to 60 mg daily and gradually escalated. Doses of 1 g have been administered safely, at least in the short term. The use of ketamine infusions have been previously well established to produce analgesia, and they have been recently reintroduced into clinical use as brief infusions for the management of patients with refractory neuropathic pain. Further studies are necessary to demonstrate the safety and efficacy of these treatment approaches in long-term management for chronic neuropathic pain.

Calcitonin has been reported to provide analgesia in patients with sympathetically maintained pain and in the management of acute phantom pain.¹⁴⁹ The mechanism underlying these analgesic effects is unknown, but it has suggested the empirical use of calcitonin in patients with refractory neuropathic pain. The clinical anecdotal literature suggests that patients be treated initially with a low dose, after initial skin testing to rule out hypersensitivity to this agent, with gradual escalation to a range of 100 to 200 IU/d. Its use chronically has not been assessed, and further studies are necessary to define its place in the treatment of patients with neuropathic pain.

ADJUVANTS FOR BONE PAIN. Metastatic disease to bone is the most common cause of pain in patients with cancer. Analgesic drug therapy is commonly used to manage the pain during the initial treatment with either chemotherapy or radiation therapy. Multifocal metastatic bone disease that is refractory to routine treatments may benefit from the use of a series of agents, including the bisphosphonate compounds, gallium nitrate, calcitonin, and strontium 89.¹⁵⁰⁻¹⁵⁴ The current bisphosphonates used for the treatment of bone pain include pamidronate and clonidronate.¹⁵⁰⁻¹⁵³ Pamidronate is usually administered as a brief infusion in a starting dose of 60 mg. Analgesia, if it occurs, usually appears within days, but may accrue for many weeks with repeated infusions. Clonidronate may be administered orally and has been demonstrated to be efficacious in patients with breast cancer and multiple myeloma. Calcitonin has also been reported anecdotally to be useful in patients with malignant bone pain, but the appropriate dose and dosing frequency have not been well defined.¹⁵⁴ Gallium nitrate has also been used with some efficacy in patients with metastatic bone pain, but the limited experience has not well defined appropriate dosing guidelines.¹⁵⁵ Strontium 89 is a bone-seeking radiopharmaceutical, recognized as useful in the treatment of bone pain secondary to metastatic disease.¹⁵⁶ It is indicated in patients with refractory multifocal pain due to osteoblastic lesions who have a life expectancy greater than three months, who have sufficient bone marrow

rally). Hemangioma regression with interferon- α -2a is less dramatic than in cases in which the lesion is highly responsive to corticosteroids.

Interferon α -2a is less toxic in infants and children than in adults, and its toxic effects are usually reversible. These include fever, transient neutropenia, anemia, and elevation of liver enzymes.⁷² Most infants on interferon α -2a seem to gain weight and grow normally in contrast with infants on prolonged corticosteroid therapy. A more problematic possible adverse reaction is increased motor tone of the lower extremities reported in some children receiving interferon for laryngeal papillomas.⁹⁸ A neurologic developmental evaluation is currently advised before beginning interferon therapy, and periodic assessments during and after therapy. In my own experience to date, of 58 infants treated with interferon α -2a for life-threatening or sight-threatening hemangiomas, 5 had a delay in walking, 2 of whom recovered after discontinuation of therapy. Combining corticosteroids and interferon α -2a therapy has shown no advantage and may increase toxicity. Interferon- α -2b has also been used successfully,⁸⁹ although one failure has been reported.⁹⁹

I measured bFGF in the urine of hemangioma patients, because of the overexpression of bFGF (and VEGF) in growing hemangiomas⁷⁷ and because bFGF is elevated in the serum and urine of a wide variety of cancer patients.¹⁰⁰ I found abnormally elevated levels (more than 5 to 10 times normal) of bFGF in patients with hemangiomas, and these levels are being used to guide therapy and to distinguish between hemangiomas and vascular malformations in an ongoing prospective study (Folkman and coworkers, unpublished). These results are complemented by those of Singh and coworkers,¹⁰¹ who found that interferon- α downregulates mRNA and protein for bFGF, and by the studies of Fidler (personal communication) that keratinocytes overlying growing hemangiomas are deficient in interferon- β , but that interferon- β levels return to normal when the hemangioma involutes. Taken together, these data suggest that hemangiomas may be associated with a deficiency of an angiogenesis suppressor and that treatment with interferon- α -2a is analogous to replacement therapy. Expression of bFGF in human bladder carcinoma cells was also downregulated by interferon- α .¹⁰² This suggests that in those bladder cancers responsive to interferon- α the mechanism may be due in part to inhibition of angiogenesis as a result of downregulation of bFGF production.

From these clinical studies, some general guidelines about antiangiogenic therapy have emerged:

1. Long-term therapy is necessary. While the regression of large serious hemangiomas was markedly accelerated (1 year, in contrast with 5 to 12 years by spontaneous involution), antiangiogenic therapy is a relatively slower process than cytotoxic therapy of a tumor.
2. Antiangiogenic therapy should not be interrupted, because of the capacity of microvessels to rapidly regrow. In a few patients in whom the schedule for interferon- α was changed from a daily injection to every other day, the hemangioma resumed growth and platelet trapping worsened.
3. Drug resistance does not appear to be a problem even with long-term therapy.
4. It was not uncommon to observe continued, although slowed, growth of a large hemangioma (e.g., a hemangi-

oma of approximately 0.25 kg on the back of a 3.5 kg baby) for up to 2 weeks after interferon therapy was started, before the accelerated involution began. This could be the result of storage sites of bFGF in the extracellular matrix. Nevertheless, the implication is that in a clinical trial of an angiogenesis inhibitor against a tumor, such a pattern would be interpreted as "progression of disease," and the inhibitor would be discontinued before its efficacy could be demonstrated.

CLINICAL TRIALS OF THE FIRST "SELECTIVE" ANGIOGENESIS INHIBITOR, TNP-470 (AGM-1470)

In 1985, Donald Ingber, in my laboratory, discovered that a fungal contaminant, *Aspergillus fumigatus fresenius* inhibited growth of capillary endothelial cells in culture.⁴ The active compound secreted by the fungus was fumagillin, an old amebocide. It inhibited endothelial proliferation in vitro and angiogenesis in vivo. A synthetic analogue of fumagillin, angiogenesis modulator-1470 (AGM-1470) was a more potent angiogenesis inhibitor than the parent compound and was nontoxic.¹⁰³⁻¹⁰⁶ Systemic administration of AGM-1470 inhibited ocular angiogenesis in rabbits and inhibited tumors in mice, rats, and rabbits (including human tumors in athymic mice) with little or no toxicity.¹⁰⁷⁻¹¹⁰ Picomolar concentrations of AGM-1470 specifically inhibited proliferating endothelial cells, but concentrations 100 to 10,000 times higher were required to inhibit growth of most tumor cells. AGM-1470 appears to be rapidly cleared from the blood.¹¹¹ Therefore, AGM-1470 is an angiogenesis inhibitor highly selective for endothelial cells, although it is not a specific inhibitor like angiostatin.

Phase I clinical trials began in late 1992 in patients with cancer and Kaposi's sarcoma. [The clinical preparation is TNP-470 (Takeda Neoplastic Product-470).] FDA-approved dose-escalation studies were then extended to the treatment of metastatic carcinoma of the prostate and cervix, and other solid tumors. Therapy was administered intravenously for 1 h every other day. At this writing, approximately 170 patients with advanced cancer have been treated in phase I trials in different cancer centers in the United States. Kudelka recently reported a dose-escalation study (from 9.3 mg/m² to 71.25 mg/m²) in 18 patients with advanced squamous cell carcinoma of the cervix, not otherwise curable.¹¹² TNP was infused every other day for 14 doses, followed by a 14-day rest period. One complete response (CR) was noted at 71.25 mg/m², a dose level at which dose-limiting CNS toxicity was also observed. The complete response occurred after 18 weeks. Bilateral lung metastases (biopsy proved to be cervical carcinoma) had disappeared by this time. The complete response has continued for 1 year and 5 months at this writing, and the patient continues on therapy without toxicity.

The lessons from this study are as follows:

- The long period for efficacy to be observed
- The absence of drug resistance over this period
- The general lack of toxicity (even though this patient was on a dose that was at the level of dose-limiting toxicity).

OTHER ANGIOGENESIS INHIBITORS IN CLINICAL TRIALS

Other angiogenesis inhibitors have entered clinical trials for patients with advanced cancer. These include carboxyamino-

azole, a signal transduction inhibitor which blocks calcium influx¹¹³; Tecogalen (DS4152), a sulfated polysaccharide¹¹⁴; L-nomide (quinoline-3-carboxamide)¹¹⁵; thalidomide⁶⁵; BB2516 (British Biotechnology 2516), a metalloproteinase inhibitor which also inhibits angiogenesis¹¹⁶ and interleukin-12.⁷⁸ It is too early to summarize the results of these trials.

PRINCIPLES OF ANTIANGIOGENIC THERAPY FOR THE DESIGN OF CLINICAL TRIALS

When the experience with antiangiogenic therapy of tumor-bearing animals is taken together with data from the early clinical trials of angiogenesis inhibitors in patients with advanced cancer, certain general guidelines emerge which may be helpful in the design of clinical trials.

First, the goal of antiangiogenic therapy is to restore a focus of migrating and proliferating capillary endothelial cells to their normal resting state. Thus, the more *selective* an angiogenesis inhibitor is for endothelial cells, the less likely it is to cause bone marrow suppression, gastrointestinal symptoms, or hair loss. This is not to say that such drugs would have no other actions and not produce side effects. For example, TNP-470 has dose-limiting CNS toxicity. However, angiostatin is a *specific* inhibitor of endothelial cell proliferation and has no effect on other cell types.¹¹ This narrow specificity may contribute to its complete lack of toxicity in animals at this writing.

Second, optimal antiangiogenic therapy appears to require treatment for months to a year or more, without a break. Regression or involution of a rapidly growing capillary bed is a slower process than lysis of tumor cells. Thus, in the design of clinical trials, antiangiogenic therapy may need longer periods without a break than do conventional cytotoxic agents. Therefore, an endpoint for evaluation of efficacy at the beginning of a clinical trial may need to be "stable disease," and should take into account the fact that, during antiangiogenic therapy, tumor growth may slow before the onset of a cytostatic effect. Otherwise, an angiogenesis inhibitor could be withdrawn from a clinical trial prematurely, and the long-term or apparent cumulative effect would be missed. Partial responses (PR) and complete responses, as observed with cytotoxic therapy, may not be observed with angiogenesis inhibitors currently available (e.g., TNP-470 or interferon- α), especially when these inhibitors are tested as single agents. If these responses do occur, many months of treatment may be required. In contrast, angiostatin can cause regression of large tumors in animals, and one can speculate that angiostatin or inhibitors of equivalent high potency may be able to induce partial or complete response in human tumors.

Third, resistance to angiogenesis inhibitors has not been a major problem in long-term animal studies or in clinical trials to date. Babies with large hemangiomas of the mediastinum or liver, who were treated with interferon α -2a daily for up to a year, did not develop drug resistance. Of interest, antiangiogenic therapy has been proposed as a strategy to circumvent acquired resistance to anticancer agents.¹¹⁷

Fourth, a combination of antiangiogenic and cytotoxic therapy may be more effective than either type alone.¹¹⁸ In tumor-bearing animals, such combinations can be curative, whereas either agent alone is only inhibitory.⁴⁹ An angiogenesis inhibitor such as AGM-1470 (TNP-470) can significantly decrease DNA synthesis in endothelial cells in a tumor bed, whereas

cytotoxic agents such as Adriamycin and cisplatin do not.¹¹⁹ These results suggest that therapy directed against both the endothelial cell and tumor cell compartments of a tumor is more effective than therapy only against tumor cells. Radiotherapy is also potentiated by antiangiogenic therapy in tumor-bearing animals, in part by decreasing tumor hypoxia.¹²⁰

Finally, certain common misconceptions may impede the appropriate design of a clinical trial, as follows:

- It is often assumed that only "highly vascularized" tumors can be treated with an angiogenesis inhibitor. This misconception is based on the gross appearance of tumors after removal. Some large tumors (larger than 2 to 3 cm) appear white and others appear to be red. The white tumors are assumed to be avascular, but in fact it is their high interstitial pressure which causes vascular compression. At the microscopic level, virtually all tumors reveal a similar neovascular capillary network with only small variations in intercapillary distances and arteriovenous shunts.
- Another common assumption is that large "established" tumors cannot be treated by antiangiogenic therapy. In fact, the new microvessels within a tumor have a high turnover rate, and any interference with the angiogenic stimulus which maintains that high replication rate of endothelium will lead to gradual involution of microvessels. The feeder vessels may be "established" but the neovascular networks are not.
- It is often assumed that only malignant tumors and not benign tumors can be treated by antiangiogenic therapy. In fact, the presence of angiogenesis does not distinguish between a benign and a malignant tumor. Adrenal adenomas are benign, yet are highly neovascularized, and these tumors appear unable to take advantage of the new vessels they have induced. One can speculate that certain slow-growing "benign" tumors, such as giant cell tumors of the bone, or fibromas, or even benign prostatic hypertrophy, may be candidates for antiangiogenic therapy.

The hypothesis that tumor growth is angiogenesis dependent was first introduced in 1971.² During the past decade, formal proof of principle for this idea has been established in the laboratory. It is hoped that in the next decade proof of principle in the clinic may become a reality.

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